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BY

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NOTE.

The formula for Hæmatin given in § 351, p. 568, is the old one of Hoppe-Seyler; that given in § 447, p. 744, is the more recent and probably more correct one of Nencki and Sieber.

It was not observed until too late that in the diagram of the nerves of the alimentary canal in the dog § 276, p. 466, *twelve* dorsal nerves had been represented. The figure, as stated, makes no pretence to anatomical exactness; but it would have been better to represent either thirteen or fifteen (see § 412) dorsal nerves.

ERRATA.

p. 430, l. 9,	*for*	§ 237	*read*	§ 238.
p. 434, l. 23,	,,	§ 232	,,	§ 233.
p. 462, l. 3, from bottom	,,	§ 266	,,	§ 265.

BOOK II.

THE TISSUES OF CHEMICAL ACTION WITH THEIR RESPECTIVE MECHANISMS. NUTRITION.

37

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CHAPTER I.

THE TISSUES AND MECHANISMS OF DIGESTION.

§ 196. THE food in passing along the alimentary canal is subjected to the action of certain juices supplied by the secretory activity of the epithelium cells which line the canal itself or which form part of its glandular appendages. These juices (viz. saliva, gastric juice, bile, pancreatic juice, and the secretions of the small and large intestines), poured upon and mingling with the food, produce in it such changes, that from being largely insoluble it becomes largely soluble, or otherwise modify it in such a way that the larger part of what is eaten passes into the blood, either directly by means of the capillaries of the alimentary canal or indirectly by means of the lacteal system, while the smaller part is discharged as excrement.

Those parts of the food which are thus digested, absorbed and made use of by the body, are spoken of as *food-stuffs* (they have also been called *alimentary principles*) and may be conveniently divided into four great classes.

1. *Proteids.* We have previously (§ 15) spoken of the chief characters of this class, and have dealt with several members in treating of blood and muscle. We may here repeat that in general composition they contain in 100 parts by weight "in round numbers" rather more than 15 parts of nitrogen, rather more than 50 parts of carbon, about 7 parts of hydrogen, and rather more than 20 parts of oxygen; though essentially the nitrogenous bodies of food and of the body they are made up of carbon to the extent of more than half their weight.

The nitrogenous body *gelatin*, which occurs largely in animal food, and some other bodies of less importance, while more closely allied to proteid bodies than to any other class of organic substances, differ considerably from proteids in composition and especially in their behaviour in the body; they are not of sufficient importance to form a class by themselves.

2. *Fats,* frequently but erroneously called Hydrocarbons. These vary very widely in chemical composition, ranging from such a comparatively simple fat as butyrin to the highly complex lecithin (§ 71); they all possess, in view of the oxidation of both their carbon and their hydrogen, a large amount of potential energy.

3. *Carbo-hydrates,* or sugars and starches. These possess weight for weight relatively less potential energy than do fats; they already contain in themselves a large amount of combined oxygen and when completely oxidised give out, weight for weight, less heat than do fats.

4. *Saline or Mineral Bodies,* and *Water.* These salts are for the most part inorganic salts; and this class differs from the three preceding classes in as much as the usefulness of its members to the body lies not so much in the amount of energy which may be given out by their oxidation, as in the various influences which, by their presence, they exercise on the metabolic events of the body.

These several food-stuffs are variously acted upon in the several parts of the alimentary canal, and we may distinguish, as the food passes along the digestive tract three main stages: digestion in the mouth and stomach, digestion in the small intestine, and digestion in the large intestine. In many animals the first stage is, to a large extent, preparatory only to the second which in all animals is the stage in which the food undergoes the greatest change; in the third stage the changes begun in the previous stages are completed, and this stage is especially characterised by the absorption of fluid from the interior of the alimentary canal.

It will be convenient to study these stages, more or less apart, though not wholly so, and it will also be convenient to consider the whole subject of digestion under the following heads:—

First, the characters and properties of the various juices, and the changes which they bring about in the food eaten.

Secondly, the nature of the processes by means of which the epithelium cells of the various glands and various tracts of the canal are able to manufacture so many various juices out of the common source, the blood, and the manner in which the secretory activity of the cells is regulated and subjected to the needs of the economy.

Thirdly, the mechanisms, here as elsewhere chiefly of a muscular nature, by which the food is passed along the canal, and most efficiently brought into contact with the several juices.

Fourthly and lastly, the means by which the nutritious digested material is separated from the undigested or excremental material, and absorbed into the blood.

SEC. 1. THE CHARACTERS AND PROPERTIES OF SALIVA AND GASTRIC JUICE.

Saliva.

§ 197. Mixed saliva, as it appears in the mouth, is a thick, glairy, generally frothy and turbid fluid. Under the microscope it is seen to contain, besides the molecular débris of food, bacteria and other organisms (frequently cryptogamic spores), epithelium-scales, mucus-corpuscles and granules, and the so-called salivary corpuscles. Its reaction in a healthy subject is alkaline, especially when the secretion is abundant. When the saliva is scanty, or when the subject suffers from dyspepsia, the reaction of the mouth may be acid. Saliva contains but little solid matter, on an average probably about ·5 p. c., the specific gravity varying from 1·002 to 1·006. Of these solids, rather less than half, about ·2 p.c., are salts (including at times a minute quantity of potassium sulphocyanate). The organic bodies which can be recognised in it are globulin and serum-albumin (see §§ 16, 17) found in small quantities only, other obscure bodies occurring in minute quantity, and *mucin*; the latter is by far the most conspicuous organic constituent, the glairiness or ropiness of mixed and other kinds of saliva being due to its presence.

Mucin. If acetic acid be cautiously added to mixed saliva the viscidity of the saliva is increased, and on further addition of the acid a semi-opaque ropy mass separates out, leaving the rest of the saliva limpid. This ropy mass, which is mucin, if stirred carefully with a glass rod, shrinks, becoming opaque, clings to the glass rod and may be thus removed from the fluid. If the quantity of mucin be small and the saliva be violently shaken or stirred while the acid is being added, the mucin is apt to be precipitated in flakes, and may then be separated by filtration. It may be added that the precipitation of mucin by acid is greatly influenced by the presence of sodium chloride and other salts; thus after the addition of sodium chloride acetic acid even in considerable excess will not cause a precipitate of mucin.

Mucin, thus prepared and purified by washing with acetic acid, swells out in water, without actually dissolving; it will however dissolve into a viscid fluid readily in dilute (0·1 p.c.) solutions of potassium hydrate, more slowly in solutions of alkaline salts. In order to filter a mucin solution, great dilution with water is necessary.

Mucin is precipitated by strong alcohol and by various metallic salts; it may also be precipitated by dilute mineral acids, but the precipitate is then soluble in excess of the acid.

Mucin gives the three proteid reactions mentioned in § 15, but it is a very complex body, more complex even than proteids, for by treatment with dilute mineral acids, and in other ways, it may be converted into some form of proteid (acid-albumin when dilute mineral acid is used), while at the same time there is formed a body which appears to be a carbohydrate and resembles a sugar in having the power of reducing cupric sulphate solutions. Solutions of mucin moreover on mere keeping are apt to lose their viscidity and to become converted into a proteid not unlike the body peptone, which as we shall see is the result of gastric digestion, and into a reducing body. Several kinds of mucin appear to exist in various animal bodies, but they seem all to agree in the character that they can by appropriate treatment be split up into a proteid of some kind and into a carbohydrate or allied body.

§ 198. The chief purpose served by the saliva in digestion is to moisten and soften the food, and to assist in mastication and deglutition. In some animals this is its only function. In other animals and in man it has a specific solvent action on some of the food-stuffs. Such minerals as are soluble in slightly alkaline fluids are dissolved by it. On fats it has no effect save that of producing a very feeble emulsion. On proteids it has also no specific action, though pieces of meat, cooked or uncooked, appear greatly altered after they have been masticated for some time; the chief alteration however which thus takes place is a change in the haemoglobin, and a general softening of the muscular fibres by aid of the alkalinity of the saliva. Of course when particles of food are retained for a long time in the mouth, as in the interstices, or in cavities of the teeth, the bacteria or other organisms which are always present in the mouth may produce much more profound changes, but these are not the legitimate products of the action of saliva. The characteristic property of saliva is that of converting starch into some form of sugar.

Action of Saliva on Starch. If to a quantity of boiled starch, which is always more or less viscid and somewhat opaque or turbid, a small quantity of saliva be added, it will be found after a short time that an important change has taken place, inasmuch as the mixture has lost its previous viscidity and become thinner and more transparent. In order to understand this change, the reader must bear in mind the existence of the following bodies all belonging to the class of carbohydrates.

1. *Starch,* which forms with water not a true solution but a more or less viscid mixture, and gives a characteristic blue colour with iodine. The formula is $C_6H_{10}O_5$ or more correctly $(C_6H_{10}O_5)_n$ since the molecule of starch is some multiple (n being not less than 5) of the simpler formula. A kind of starch, known as *soluble starch,* while giving a blue colour with iodine, forms, unlike ordinary starch, a clear solution.

2. *Dextrins,* differing from starch in forming a clear solution. Of these there are at least two; one *erythrodextrin,* often spoken of simply as dextrin, giving a port-wine red colour with iodine, and a second, *achroodextrin,* which gives no colour at all with iodine. The formula for dextrin is the same as that for starch, but has a smaller molecule and might be represented by $(C_6H_{10}O_5)_{n'}$.

3. *Dextrose,* also called glucose or grape-sugar, giving no colouration with iodine, but characterised by the power of reducing cupric and other metallic salts; thus, when dextrose is boiled with a fluid known as Fehling's fluid, which is a solution of hydrated cupric oxide in an excess of caustic alkali and double tartrate of sodium and potassium, the cupric oxide is reduced and a red or yellow deposit of cuprous oxide is thrown down. This reaction serves with others as a convenient test for dextrose. Neither starch nor that commonest form of sugar known as cane-sugar, give this reaction; whether the dextrins do is doubtful. The formula for dextrose is $C_6H_{12}O_6$; it is more simple than that of starch or dextrin and contains an additional H_2O for every C_6. Unlike starch and dextrin it can be obtained in a crystalline form, either from aqueous solutions (it being readily soluble in water), in which case the crystals contain water of crystallisation, or from its solutions in alcohol (in which it is sparingly soluble), in which case the crystals have no such water of crystallisation. Solutions of dextrose have a marked dextrorotatory power over rays of light.

4. *Maltose,* very similar to dextrose, and like it capable of reducing cupric salts. The formula is somewhat different, being $C_{12}H_{22}O_{11}$. Besides this, it differs from dextrose chiefly in its smaller reducing power, *i.e.* a given weight will not convert so much cupric oxide into cuprous oxide as will the same weight of dextrose, and in having a stronger rotatory action on rays of light. Like dextrose it can be crystallised, the crystals from aqueous solutions containing water of crystallisation.

Now when a quantity of starch is boiled with water we may recognise in the viscid imperfect solution, on the one hand the presence of starch, by the blue colour which the addition of iodine gives rise to, and on the other hand the absence of sugar (maltose, dextrose), by the fact that when boiled with Fehling's fluid no reduction takes place and no cuprous oxide is precipitated.

If however the boiled starch be submitted for a while to the action of saliva, especially at a somewhat high temperature such as 35° or 40° C., it is found that the subsequent addition of iodine gives no blue colour at all, or very much less colour, shewing that the starch has disappeared or diminished; on the other hand the mixture readily gives a precipitate of cuprous oxide when boiled with Fehling's fluid, shewing that maltose or dextrose is present. That is to say the saliva has converted the starch into maltose or dextrose. The presence of the previously absent sugar may also be shewn by fermentation and by the other tests for sugar. Moreover, if an adequately large quantity of starch be subjected to the charge, the sugar formed may be isolated, and its characters determined. When this is done it is found that while some dextrose is formed the greater part of the sugar which appears is in the form of maltose. As is well known starch may by the action of dilute acid be converted into dextrin, and by further action into sugar; but the sugar thus formed is always wholly dextrose, and not maltose at all. The action of saliva in this respect differs from the action of dilute acid.

While the conversion of the starch by the saliva is going on the addition of iodine frequently gives rise to a red or violet colour instead of a pure blue, but when the conversion is complete no coloration at all is observed. The appearance of this red colour indicates the presence of dextrin (erythrodextrin); the violet colour is due to the red being mixed with the blue of still unchanged starch.

The appearance of dextrin shews that the action of the saliva on the starch is somewhat complex; and this is still further proved by the fact that even when the saliva has completed its work the whole of the starch does not reappear as maltose or dextrose. A considerable quantity of the other dextrin (achroodextrin) always appears and remains unchanged to the end; and there are probably several other bodies also formed out of the starch, the relative proportions varying according to circumstances. The change therefore, though perhaps we may speak of it in a general way as one of hydration, cannot be exhibited under a simple formula, and we may rest content for the present with the statement that starch when subjected to the action of saliva is converted chiefly into the sugar known as maltose with a comparatively small quantity of dextrose and to some extent into achroodextrin (erythrodextrin appearing temporarily only in the process), other bodies on which we need not dwell being formed at the same time.

Raw unboiled starch undergoes a similar change but at a much slower rate. This is due to the fact that in the curiously formed starch grain the true starch, or *granulose*, is invested with coats of *cellulose*. This latter material, which requires previous treatment with sulphuric acid before it will give the blue reaction on the addition of iodine, is apparently not acted upon by saliva.

Hence the saliva can only get at the granulose by traversing the coats of cellulose, and the conversion of the former is thereby much hindered and delayed.

§ **199**. The conversion of starch into sugar, and this we may speak of as the amylolytic action of saliva, will go on at the ordinary temperature of the atmosphere. The lower the temperature the slower the change, and at about 0° C. the conversion is indefinitely prolonged. After exposure to this cold for even a considerable time the action recommences when the temperature is again raised. Increase of temperature up to about 35°—40°, or even a little higher, favours the change, the greatest activity being said to be manifested at about 40°. Much beyond this point, however, increase of temperature becomes injurious, markedly so at 60° or 70°; and saliva which has been boiled for a few minutes not only has no action on starch while at that temperature, but does not regain its powers on cooling. By being boiled, the amylolytic activity of saliva is permanently destroyed.

The action of saliva on starch is most rapid when the reaction of the mixture is neutral or nearly so; it is hindered or arrested by a distinctly acid reaction. Indeed the presence of even a very small quantity of free acid, at all events of hydrochloric acid, at the temperature of the body not only suspends the action but speedily leads to permanent abolition of the activity of the juice. The bearing of this will be seen later on.

The action of saliva is hampered by the presence in a concentrated state of the product of its own action, that is, of sugar. If a small quantity of saliva be added to a thick mass of boiled starch, the action will after a while slacken, and eventually come to almost a stand-still long before all the starch has been converted. On diluting the mixture with water, the action will recommence. If the products of action be removed as soon as they are formed, by dialysis for example, a small quantity of saliva will, if sufficient time be allowed, convert into sugar a very large, one might almost say an indefinite, quantity of starch. Whether the particular constituent on which the activity of saliva depends is at all consumed in its action has not at present been definitely settled.

On what constituent do the amylolytic virtues of saliva depend?

If saliva, filtered and thus freed from much of its mucin and from other formed constituents, be treated with ten or fifteen times its bulk of alcohol, a precipitate is formed containing besides other substances all the proteid matters. Upon standing under the alcohol for some time (several days), the proteids thus precipitated become coagulated and insoluble in water. Hence, an aqueous extract of the precipitate, made after this interval, contains very little proteid material; yet it is exceedingly active. Moreover by other more elaborate methods there may be obtained from saliva solutions which appear to be almost entirely free from proteids and yet are intensely amylolytic. But even these probably contain other bodies besides the really active constituent. Whatever the active substance be in itself, it exists in such extremely small quantities that it has never yet been satisfactorily isolated; and indeed the only clear evidence we have of its existence is the manifestation of its peculiar powers.

The salient features of this body, this amylolytic agent, which we may call *ptyalin*, are then:—1st, its presence in minute and almost inappreciable quantity. 2nd, the close dependence of its activity on temperature. 3rd, its permanent and total destruction by a high temperature and by various chemical reagents. 4th, the want of any clear proof that it itself undergoes any change during the manifestation of its powers; that is to say, the energy necessary for the transformation which it effects *does not come out of itself;* if it is at all used up in its action, the loss is rather that of simple wear and tear of a machine than that of a substance expended to do work. 5th, the action which it induces is probably of such a kind (splitting up of a molecule with assumption of water) as is effected by that particular class of agents called "hydrolytic."

These features mark out the amylolytic active body of saliva as belonging to the class of *ferments*[1]; and we may henceforward speak of the amylolytic ferment of saliva. The fibrin-ferment (§ 20) is so called because its action in many ways resembles that of the ferment of which we are now speaking.

§ **200**. Mixed saliva, whose properties we have just discussed, is the result of the mingling in various proportions of saliva from the parotid, submaxillary, and sublingual glands with the secretion from the buccal glands. These constituent juices have their own special characters, and these are not the same in all animals. Moreover in the same individual the secretion differs in composition and properties according to circumstances; thus, as we shall see in detail hereafter, the saliva from the submaxillary gland secreted under the influence of the chorda tympani nerve is different from that which is obtained from the same gland by stimulating the sympathetic nerve.

In man pure parotid saliva may easily be obtained by introducing a fine cannula into the opening of the Stenonian duct, and submaxillary saliva, or rather a mixture of submaxillary and sublingual saliva, by similar catheterisation of the Whartonian duct. In animals the duct may be dissected out and a cannula introduced.

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[1] Ferments may, for the present at least, be divided into two classes, commonly called *organised* and *unorganised*. Of the former, yeast may be taken as a well-known example. The fermentative activity of yeast which leads to the conversion of sugar into alcohol, is dependent on the life of the yeast-cell. Unless the yeast-cell be living and functional, fermentation does not take place; when the yeast-cell dies fermentation ceases; and no substance obtained from the fluid parts of yeast, by precipitation with alcohol or otherwise, will give rise to alcoholic fermentation. The salivary ferment belongs to the latter class; it is a substance, not a living organism like yeast. It may be added however that possibly the organised ferment, the yeast for instance, produces its effect by means of an ordinary unorganised ferment which it generates, but which is immediately made away with.

Parotid saliva in man is clear and limpid, not viscid; the reaction of the first drops secreted is often acid, the succeeding portions, at all events when the flow is at all copious, are alkaline; that is to say the natural secretion is alkaline, but this may be obscured by acid changes taking place in the fluid which has been retained in the duct, possibly by the formation of an excess of carbonic acid. On standing, the clear fluid becomes turbid from a precipitate of calcic carbonate, due to an escape of carbonic acid. It contains globulin and some other forms of albumin, with little or no mucin. Potassium sulphocyanate may also sometimes be detected, but structural elements are absent.

Submaxillary saliva, in man and in most animals, differs from parotid saliva in being more alkaline and, from the presence of mucin, more viscid; it contains salivary corpuscles, that is bodies closely resembling if not identical with leucocytes, and, often in abundance, amorphous masses. The so-called chorda saliva in the dog, that is to say saliva obtained by stimulating the chorda tympani nerve, (of which we shall presently speak), is under ordinary circumstances thinner and less viscid, contains less mucin, and fewer structural elements, than the so-called sympathetic saliva, which is remarkable for its viscidity, its structural elements, and for its larger total of solids.

Sublingual saliva is more viscid, and contains more salts (in the dog about 1 p.c.), than the submaxillary saliva.

The action of saliva varies in intensity in different animals. Thus in man, the pig, the guinea-pig, and the rat, both parotid and submaxillary and mixed saliva are amylolytic; the submaxillary saliva being in most cases more active than the parotid. In the rabbit, while the submaxillary saliva has scarcely any action, that of the parotid is energetic. The saliva of the cat is much less active than the above; that of the dog is still less active, indeed is almost inert. In the horse, sheep, and ox, the amylolytic powers of either mixed saliva, or of any one of the constituent juices, are extremely feeble.

Where the saliva of any gland is active, an aqueous infusion of the same gland is also active. The importance and bearing of this statement will be seen later on. From the aqueous infusion of the gland, as from saliva itself, the ferment may be approximately isolated. In some cases at least some ferment may be extracted from the gland even when the secretion is itself inactive. In fact a ready method of preparing a highly amylolytic liquid tolerably free from proteid and other impurities, is to mince finely a gland known to have an active secretion, such for instance as that of a rat, to dehydrate it by allowing it to stand under absolute alcohol for some days, and then, having poured off most of the alcohol, and removed the remainder by evaporation at a low temperature to cover the pieces of gland with strong glycerine. Though some of the ferment appears to be destroyed by the alcohol a mere drop of such a glycerine extract rapidly converts starch into sugar.

Gastric Juice.

§ **201**. There is no difficulty in obtaining what may fairly be considered as a normal saliva; but there are many obstacles in the way of determining the normal characters of the secretion of the stomach. When no food is taken the stomach is at rest and no secretion takes place. When food is taken, the characters of the gastric juice secreted are obscured by the food with which it is mingled. The gastric membrane may it is true be artificially stimulated, by touch for instance, and a secretion obtained. This we may speak of as gastric juice, but it may be doubted whether it ought to be considered as normal gastric juice. And indeed as we shall see even the juice, which is poured into the stomach during a meal, varies in composition as digestion is going on. Hence the characters which we shall give of gastric juice must be considered as having a general value only.

Gastric juice, obtained in as normal a condition as possible from the healthy stomach of a fasting dog, by means of a gastric fistula, is a thin almost colourless fluid with a sour taste and odour.

In the operation for gastric fistula, an incision is made through the abdominal walls, along the *linea alba*, the stomach is opened, and the lips of the gastric wound securely sewn to those of the incision in the abdominal walls. Union soon takes place, so that a permanent opening from the exterior into the inside of the stomach is established. A tube of proper construction, introduced at the time of the operation, becomes firmly secured in place by the contraction of healing. Through the tube the contents of the stomach can be received, and the mucous membrane stimulated at pleasure.

When obtained from a natural fistula in man, its specific gravity has been found to differ little from that of water, varying from 1·001 to 1·010, and the amount of solids present to be correspondingly small. In animals, pure gastric juice seems to be equally poor in solids, the higher estimates which some observers have obtained being probably due to admixture with food, &c.

Of the solid matters present about half are inorganic salts, chiefly alkaline (sodium) chlorides, with small quantities of phosphates. The organic material consists of pepsin, a body to be described immediately, mixed with other substances of undetermined nature. In a healthy stomach gastric juice contains a very small quantity only of mucin, unless some submaxillary saliva has been swallowed.

The reaction is distinctly acid, and the acidity is normally due to free hydrochloric acid. This is shewn by various proofs, among which we may mention the conclusive fact that the amount of chlorine present in gastric juice is more than would suffice to form chlorides with all the bases present, and that the excess if regarded as existing in the form of hydrochloric acid corresponds exactly to the quantity of free acid present. Lactic and butyric and other acids when present are secondary products, arising either by their respective fermentations from articles of food, or from the decomposition of their alkaline or other salts. In man the amount of free hydrochloric acid in healthy juice may be stated to be about ·2 per cent., but in some animals it is probably higher.

§ **202**. On starch gastric juice has no amylolytic action; on the contrary when saliva is mixed with gastric juice any amylolytic ferment which may be present in the former is at once prevented from acting by the acidity of the mixture. Moreover in a very short time, especially at the temperature of the body, the amylolytic ferment is destroyed by the acid so that even on neutralisation the mixture is unable to convert starch into sugar.

On dextrose healthy gastric juice has no effect. And its power of inverting cane-sugar seems to be less than that of hydrochloric acid diluted to the same degree of acidity as itself. In an unhealthy stomach however containing much mucus, the gastric juice is very active in converting cane-sugar into dextrose. This power seems to be due to the presence in the mucus of a special ferment, analogous to, but quite distinct from, the ptyalin of saliva. An excessive quantity of cane-sugar introduced into the stomach causes a secretion of mucus, and hence provides for its own conversion.

On fats gastric juice has at most a limited action. When adipose tissue is eaten, the chief change which takes place in the stomach is that the proteid and gelatiniferous envelopes of the fat-cells are dissolved, and the fats set free. Though there is experimental evidence that emulsion of fats to a certain extent does take place in the stomach, the great mass of the fat of a meal is not so changed.

Such minerals as are soluble in free hydrochloric acid are for the most part dissolved; though there is a difference in this and in some other respects between gastric juice and simple free hydrochloric acid diluted with water to the same degree of acidity as the juice, the presence either of the pepsin or of other bodies apparently modifying the solvent action of the acid.

The essential property of gastric juice is the power of dissolving proteid matters, and of converting them into a substance called peptone.

Action of gastric juice on proteids. The results are essentially the same whether natural juice obtained by means of a fistula or artificial juice, *i.e.* an acid infusion of the mucous membrane of the stomach, be used.

Artificial gastric juice may be prepared in any of the following ways.

1. The mucous membrane of a pig's or dog's stomach is removed from the muscular coat, finely minced, rubbed in a mortar with pounded glass and extracted with water. The aqueous extract filtered and acidulated (it is in itself somewhat acid), until it has a free acidity corresponding to ·2 p.c. of hydrochloric acid, contains but little of the products of digestion such as peptone, but is fairly potent.

2. The mucous membrane similarly prepared and minced is allowed to digest at 35° C. in a large quantity of hydrochloric acid diluted to ·2 p.c. The greater part of the membrane disappears, shreds only being left, and the somewhat opalescent liquid can be decanted and filtered. The filtrate has powerful digestive (peptic) properties, but contains a considerable amount of the products of digestion (peptone, &c.), arising from the digestion of the mucous membrane itself[1].

3. The mucous membrane, similarly prepared and minced, is thrown into a comparatively large quantity of concentrated glycerine, and allowed to stand. The membrane may be previously dehydrated by being allowed to stand under alcohol, but this is not necessary, and a too prolonged action of the alcohol injures or even destroys the activity of the product. The decanted clear glycerine, in which a comparatively small quantity of the ordinary proteids of the mucous membrane are dissolved, if added to hydrochloric acid of ·2 p.c. (about 1 c.c. of the glycerine to 100 c.c. of the dilute acid are sufficient), makes an artificial juice tolerably free from ordinary proteids and peptone, and of remarkable potency, the presence of the glycerine not interfering with the results.

Before proceeding to study the action of gastric juice on proteids it will be useful to review very briefly the chief characters of the more important members of the group.

The more important proteids which we have thus far studied are: 1. *Fibrin*, insoluble in water and not really soluble (*i.e.* without change) in saline solutions. 2. *Myosin*, insoluble in water but soluble in saline solutions, provided these are not too dilute or too concentrated. 3. *Globulin* (including para-globulin, fibrinogen &c.), insoluble in water, but readily soluble in even very dilute saline solutions. 4. *Albumin, serum-albumin*, soluble in water in the absence of all salts. 5. *Acid-albumin*, into which globulins and myosin are rapidly converted by the action of dilute acids, the particular acid-albumin into which the myosin of muscle is changed being sometimes called *syntonin*. If the reagent used be not dilute acid but dilute alkali, the product is called alkali-albumin. The two bodies, acid-albumin and alkali-albumin, are very parallel in their characters, and may readily be converted the one into the other by the use of dilute alkali or dilute acid respectively. Their most important common characters are insolubility in water and in saline solutions and ready solubility in dilute acids and alkalis. 6. *Coagulated proteids.* As we have seen, when fibrin suspended in water, serum-albumin in solution, acid-albumin or alkali-albumin suspended in water, or paraglobulin suspended in water or dissolved in a dilute saline solution, are heated to a temperature, which for the whole group may be put down at about 75°—80° C., each of them becomes coagulated, and after the change is insoluble in water, saline solutions, dilute acids &c., in fact in everything but very strong acids. Myosin and fibrinogen undergo a similar change at a lower temperature, viz. about 56° C. We may, for present purposes, speak of all these proteids thus changed under the one term of coagulated proteids.

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[1] These however may be removed by concentration at 40° C. and subsequent dialysis.

To the above list we may now add two other proteids, viz.: 7. A kind of albumin which forms the great bulk of the proteid matter present in raw 'white of egg', and which, since it differs in minor characters from the albumin of blood and of the tissues, is called *egg-albumin.* 8. The peculiar proteid *casein*, an important constituent of milk. This may perhaps be regarded as a naturally occurring alkali-albumin since it has many resemblances to the artificial alkali-albumin; but for several reasons it is desirable to consider it as an independent body.

Egg-albumin like serum-albumin becomes coagulated at a temperature of about 75°—80° C., and though casein as it naturally exists in milk is not coagulated on boiling, when separated out in a special way, and suspended in water in which it is insoluble, it becomes coagulated at about 75°—80° C.

It will be observed that all these proteids form, as regards their solubilities, a descending series, in the following order. Coagulated Proteids. Fibrin. Acid-albumin with Alkali-albumin, and Casein. Myosin, Globulins. Serum-albumin with Egg-albumin.

We must now return to the action of gastric juice.

If a few shreds of fibrin, obtained by whipping blood, after being thoroughly washed and boiled and thus by the boiling coagulated, be thrown into a quantity of gastric juice, and the mixture be exposed to a temperature of from 35° to 40° C., the fibrin will speedily, in some cases in a few minutes, be dissolved. The shreds first swell up and become transparent, then gradually dissolve, and finally disappear with the exception of some granular debris, the amount of which, though generally small, varies according to circumstances. If raw, that is unboiled, uncoagulated fibrin be employed the same changes may be observed, but they take place much more rapidly.

If small morsels of coagulated albumin, such as white of egg, be treated in the same way, the same solution is observed. The pieces become transparent at their surfaces; this is especially seen at the edges, which gradually become rounded down; and solution steadily progresses from the outside of the piece inwards.

If any other form of coagulated albumin (*e.g.* precipitated acid- or alkali-albumin, suspended in water and boiled) be treated in the same way, a similar solution takes place. The readiness with which the solution is effected, will depend, *cæteris paribus*, on the smallness of the pieces, or rather on the amount of surface as compared with bulk, which is presented to the action of the juice.

Gastric juice then readily dissolves coagulated proteids, which otherwise are insoluble, or soluble only, and that with difficulty, in very strong acids.

When proteids, which are soluble in water or in dilute acid, are treated with gastric juice, no visible change takes place; but nevertheless, it is found on examination that the solutions have undergone a remarkable change, the nature of which is easily seen by contrasting it with the change effected by dilute acid alone. If raw white of egg, largely diluted with water and strained, be treated with a sufficient quantity of dilute hydrochloric acid, the opalescence or turbidity which appeared in the white of egg on dilution (and which is due to the precipitation of various forms of globulin accompanying the egg-albumin in the raw white) disappears, and a clear mixture results. If a portion of the mixture be at once boiled, a large deposit of coagulated albumin occurs. If, however, the mixture be exposed to 50° or 55° C. for some time, the amount of coagulation which is produced by boiling a specimen becomes less, and, finally, boiling produces no coagulation whatever. By neutralisation, however, the whole of the albumin (with such restrictions as the presence of certain neutral salts may cause) may be obtained in the form of acid-albumin, the filtrate after neutralisation containing no proteids at all (or a very small quantity). Thus the whole of the albumin present in the white of egg may be, in time, converted, by the simple action of dilute hydrochloric acid, into acid-albumin. Serum-albumin similarly treated undergoes, in course of time a similar conversion into acid-albumin, and we have already seen (§ 59) that solutions of myosin or of any of the globulins are with remarkable rapidity converted into acid-albumin. Thus simple dilute hydrochloric of the same degree of acidity as gastric juice, merely converts these proteids into acid-albumin, the rapidity of the change differing with the different proteids, being in some cases very slow, and requiring a relatively high temperature.

If the same white of egg or serum-albumin be treated with gastric juice instead of simple dilute hydrochloric acid, the events for some time seem the same. Thus after a while boiling causes no coagulation, while neutralisation gives a considerable precipitate of a proteid body, which, being insoluble in water and in sodium chloride solutions, and soluble in dilute alkali and acids, at least closely resembles acid-albumin. But it is found that only a portion of the proteid originally present in the white of egg or serum-albumin can thus be regained by precipitation. Though the neutralisation be carried out with the greatest care it will be found, on filtering off the neutralisation precipitate, that is the acid-albumin, that the filtrate, as shewn on employing the various tests for proteid (see § 15) or on adding an adequate quantity of strong alcohol, still contains a very considerable quantity of proteid matter; and, on the whole, the longer the digestion is carried on, the greater is the proportion borne by the proteid remaining in solution to the precipitate thrown down on neutralisation; indeed, in some cases at all events, all the proteid matter originally present remains in solution, and there is no neutralisation precipitation at all, or at most a wholly insignificant one.

§ **203**. The proteid matter, thus remaining in solution after neutralisation, differs from all the proteids which we have hitherto studied in as much as, though existing in a neutral solution, it is not coagulated by heat, like the egg-albumin or serum-albumin from which it has been produced; the solution, after the neutralisation precipitate has been filtered off, remains quite clear when boiled. The only other solutions of proteids which do not coagulate on boiling are solutions of acid or alkali-albumin; but these solutions must be acid or alkali respectively; the acid-albumin or alkali-albumin is insoluble in a neutral solution, and when simply suspended in water is readily coagulated at a temperature of 75°. This new proteid matter of which we are speaking is soluble in neutral solutions, indeed in distilled water, and can under no circumstances be coagulated by heat.

Upon examination we find that the new proteid matter thus left in solution consists of at least two distinct proteid bodies. If to the solution ammonium sulphate be added, part of the proteid matter is precipitated while part is still left in solution. The proteid body thus thrown down is called *albumose* (there are several varieties of albumose but these need not now detain us). It approaches albumin in nature by reason of the fact that it will not diffuse through membranes; that it differs however widely from that proteid is shewn by its solutions not coagulating on boiling. The body which is not thrown down by ammonium sulphate is called *peptone;* it differs from albumose in being diffusible, for it will pass through membranes. The diffusion is not nearly so rapid as that of salts, sugar, and other similar substances; indeed solutions of peptones may be freed from salts by dialysis. But it is very marked as compared with that of other proteids; these pass through membranes with the greatest difficulty, if at all. Peptone is insoluble in alcohol, and may be precipitated from its solutions by the addition of an adequate quantity of this reagent; but for this purpose a very large excess of alcohol is needed, otherwise much of the peptone remains in solution. It may be kept under alcohol for a long time without undergoing change, whereas other proteids are more or less slowly coagulated by alcohol. A useful test for peptone is furnished by the fact that a solution of peptone, mixed with a strong solution of caustic potash, gives on addition of a mere trace of cupric sulphate in the cold a *pink* colour, whereas other proteids give a *violet* colour. In applying this test however care must be taken not to add too much cupric sulphate since in that case a violet colour, deepening on boiling, that is the ordinary proteid reaction (see § 15), is obtained.

There are reasons for thinking that there are several kinds or at least more than one kind of peptone; but we may for the present regard the substance as one. For a long time albumose was confounded with peptone, and many of the commercial forms of "peptone" consist largely of albumose; indeed the two are closely allied and have many reactions in common, the most striking differences being that peptone is diffusible, while albumose is not, or hardly at all, and that peptone is not like albumose precipitated by ammonium sulphate. The amount of albumose appearing in a digestion experiment, relative to the amount of true peptone, depends on the activity of the juice, and other circumstances. We may regard albumose as a less complete product of digestion than peptone.

The precipitate thrown down by neutralisation after the action of gastric juice on egg- or serum-albumin resembles, in its general characters, acid-albumin. Since, however, it probably is distinguishable from the body or bodies produced by the action of simple acid on muscle or white of egg, it is best to reserve for it the name of *parapeptone*, which was originally applied to it.

Thus the digestion by gastric juice of solutions of egg-albumin or serum-albumin results in the conversion of all the proteids present into peptone, albumose and parapeptone, of which the first may be considered as the final and chief product, and the other two as intermediate products, occurring in varying quantity, possibly not always formed, and probably of secondary importance. When fibrin, either raw or boiled, or any form of coagulated proteid is dissolved and seems to disappear under the influence of gastric juice, the same products, peptone, albumose and parapeptone make their appearance. The same bodies result when myosin or any of the globulins are subjected to the action of the juice; and acid-albumin or alkali-albumin is similarly converted into albumose and peptone.

It is obvious that the effect of the action of the gastric juice is to change the less soluble proteid into a more soluble form, the change being either completed up to the stage of peptone, the most soluble of all proteids, or being left in part incomplete. This will be seen from the following tabular arrangement of proteids according to their solubilities.

Soluble in distilled water.

Aqueous solutions not coagulated on boiling.	
Diffusible	Peptone.
Not diffusible	Albumose.
Aqueous solutions coagulated on boiling	Albumin.

Insoluble in distilled water.

Readily soluble in dilute saline solutions (NaCl 1 per cent.)	Globulins.
Soluble only in stronger saline solutions (NaCl 5 to 10 p.c.)	Myosin.

Insoluble in dilute saline solutions.

Readily soluble in dilute acid (HCl ·1 p.c.) in the cold	Acid-albumin. Alkali-albumin. Casein.
Soluble with difficulty in dilute acid, that is at high temperature (60° C.) and after prolonged treatment only	Fibrin.
Insoluble in dilute acids, soluble only in strong acids	Coagulated Proteid.

Milk when treated with gastric juice is first of all "curdled." This is the result partly of the action of the free acid but chiefly of the special action of a particular constituent of gastric juice, of which we shall speak hereafter. The curd consists of a particular proteid matter mixed with fat; and this proteid matter is subsequently dissolved with the same appearance of peptone, albumose and parapeptone as in the case of other proteids. In fact, the digestion by gastric juice of all the varieties of proteids consists in the conversion of the proteid into peptone, with the concomitant appearance of a certain variable amount of albumose and parapeptone.

§ **204**. *Circumstances affecting gastric digestion.* The solvent action of gastric juice on proteids is modified by a variety of circumstances. The nature of the proteid itself makes a difference, though this is determined probably by physical rather than by chemical characters. Hence in making a series of comparative trials the same proteid should be used, and the form of proteid most convenient for the purpose is fibrin. If it be desired simply to ascertain whether any given specimen has any digestive powers at all, it is best to use boiled fibrin, since raw fibrin is eventually dissolved by dilute hydrochloric acid alone, probably on account of some pepsin previously present in the blood becoming entangled with the fibrin during clotting. But in estimating quantitatively the peptic power of two specimens of gastric juice under different conditions, raw fibrin prepared by Grützner's method is the most convenient.

Portions of well washed fibrin are stained with carmine and again washed to remove the superfluous colouring matter. A fragment of this coloured fibrin thrown into an active juice on becoming dissolved, gives up its colour to the fluid. Hence if the same stock of coloured fibrin be used in a series of experiments, and the same bulks of fibrin and of fluid be used in each case, the amount of fibrin dissolved may be fairly estimated by the depth of tint given to the fluid. Fibrin thus coloured with carmine may be preserved in ether.

Since, if sufficient time be allowed, even a small quantity of gastric juice will dissolve at least a very large if not an indefinite quantity of fibrin, we are led to take, as a measure of the activity of a specimen of gastric juice, not the quantity of fibrin which it will ultimately dissolve, but the rapidity with which it dissolves a given quantity.

The greater the surface presented to the action of the juice, the more rapid the solution; hence minute division and constant movement favour digestion. And this is probably, in part at least, the reason why a fragment of spongy filamentous fibrin is more readily dissolved than a solid clump of boiled white of egg of the same size. Neutralisation of the juice wholly arrests digestion; fibrin may be submitted for an almost indefinite time to the action of neutralised gastric juice without being digested. If the neutralised juice be properly acidified, it may again become active; when gastric juice however has been made alkaline, and kept for some time at a temperature of 35°, its solvent powers are not only suspended but actually destroyed. Digestion is most rapid with dilute hydrochloric acid of ·2 p.c. (the acidity of natural gastric juice). If the juice contains much more or much less free acid than this, its activity is distinctly impaired. Other acids, lactic, phosphoric, &c. may be substituted for hydrochloric; but they are not so effectual, and the degree of acidity most useful varies with the different acids. The presence of neutral salts, such as sodium chloride, in excess is injurious. The action of mammalian gastric juice is most rapid at 35°—40° C.; at the ordinary temperature it is much slower, and at about 0° C. ceases altogether. The juice may be kept however at 0° C. for an indefinite period without injury to its powers. The gastric juice of cold-blooded vertebrates is relatively more active at low temperatures than that of warm-blooded mammals or birds.

At temperatures much above 40° or 45° the action of the juice is impaired. By boiling for a few minutes the activity of the most powerful juice is irrevocably destroyed. The presence in a concentrated form of the products of digestion hinders the process of solution. If a large quantity of fibrin be placed in a small quantity of juice, digestion is soon arrested; on dilution with the normal hydrochloric acid (·2 p.c.), or if the mixture be submitted to dialysis to remove the peptones formed, and its acidity be kept up to the normal, the action recommences. By removing the products of digestion as fast as they are formed, and by keeping the acidity up to the normal, a given amount of gastric juice may be made to digest a very large quantity of proteid material. Whether the quantity is really unlimited is disputed; but in any case the energies of the juice are not rapidly exhausted by the act of digestion.

§ **205**. *Nature of the action.* All these facts go to shew that the digestive action of gastric juice on proteids, like that of saliva on starch, is a ferment-action; in other words, that the solvent action of gastric juice is essentially due to the presence in it of a ferment-body. To this ferment-body, which as yet has been only approximately isolated, the name of *pepsin* has been given. It is present not only in gastric juice but also in the glands of the gastric mucous membrane, especially in certain parts and under certain conditions which we shall study presently. The glycerine extract of gastric mucous membrane, at any rate of that which has been dehydrated, contains a minimal quantity of proteid matter, and yet is intensely peptic. Other methods, such as the elaborate one of Brücke, give us a material which, though containing nitrogen, exhibits none of the ordinary proteid reactions, and yet in concert with normal dilute hydrochloric acid is peptic in a very high degree. We seem therefore justified in asserting that pepsin is not a proteid, but it would be hazardous to make any dogmatic statement concerning a substance, obtained in so small a quantity at a time that its exact chemical characters have not yet been ascertained. At present the manifestation of peptic powers is our only safe test of the presence of pepsin.

In one important respect pepsin, the ferment of gastric juice, differs from ptyalin, the ferment of saliva. Saliva is active in a perfectly neutral medium, and there seems to be no special connection between the ferment and any alkali or acid. In gastric juice, however, there is a strong tie between the acid and the ferment, so strong that some writers speak of pepsin and hydrochloric acid as forming together a compound, pepto-hydrochloric acid.

In the absence of exact knowledge of the constitution of proteids, we cannot state distinctly what is the precise nature of the change into peptone; the various proteids differ from each other in elementary composition quite as widely as does peptone from any of them. Judging from the analogy with the action of saliva on starch, we may fairly suppose that the process is at bottom one of hydration; and this view is further suggested by the fact that peptone closely resembling, if not identical with, that obtained by gastric digestion, may be obtained by the action of strong acids, by the prolonged action of dilute acids especially at a high temperature, or simply by digestion with super-heated water in a Papin's digester, that is to say by means of agents which, in other cases produce their effects by bringing about hydrolytic changes; beyond this we cannot at present go. We may add however, as supporting the same view, the statement of some observers that peptone when treated with dehydrating agents or when simply heated to 140°—170° C. is in part reconverted into a body or bodies resembling acid-albumin or globulin.

§ **206**. All proteids, so far as we know, are converted by pepsin into peptone. Concerning the action of gastric juice on other nitrogenous substances more or less allied to proteids but not truly proteid in nature our knowledge is at present imperfect. Mucin, nuclein, and the chemical basis of horny tissues are wholly unaffected by gastric juice. The gelatiniferous tissues are dissolved by it; and the bundles and membranes of connective tissue are very speedily so far affected by it, that at a very early stage of digestion, the bundles and elementary fibres of muscle which are bound together by connective tissue fall asunder; moreover both prepared gelatine and the gelatiniferous basis of connective tissue in its natural condition, that is without being previously heated with water, are by it changed into a substance so far analogous with peptone, that the characteristic property of gelatinisation is entirely lost. Chondrin and the elastic tissues undergo a similar change. It is not clear however how far this change is due simply to the acid of gastric juice independently of the pepsin.

§ **207**. *Action of gastric juice on milk.* It has long been known that an infusion of calves' stomach, called *rennet*, has a remarkable effect in rapidly curdling milk, and this property is made use of in the manufacture of cheese. Gastric juice has a similar effect; milk when subjected to the action of gastric juice is first curdled and then digested. If a few drops of gastric juice be added to a little milk in a test tube, and the mixture exposed to a temperature of 40°, the milk will curdle into a complete clot in a very short time. If the action be continued the curd or clot will be ultimately dissolved and digested. Milk contains, besides a peculiar form, or peculiar forms of albumin, fats, milk-sugar and various salines, the peculiar proteid *casein*. In natural milk casein is present in solution, and 'curdling' consists essentially in the soluble casein being converted (or more probably as we shall see presently, split up) into an insoluble modification of casein, which as it is being precipitated carries down with it a great deal of the fat and so forms the 'curd'. Now casein is readily precipitated from milk upon the addition of a small quantity of acid, and it might be supposed that the curdling effect of gastric juice was due to its acid reaction. But this is not the case, for neutralized gastric juice, or neutral rennet, is equally efficacious.

The curdling action of rennet is closely dependent on temperature, being like the peptic action of gastric juice favoured by a rise of temperature up to about 40°. Moreover the curdling action is destroyed by previous boiling of the juice or rennet. These facts suggest that a ferment is at the bottom of the matter; and indeed, all the features of the action support this view. Moreover, as a matter of fact, a curdling ferment may be extracted by glycerine and by the other methods used for preparing ferments. The ferment however is not pepsin but some other body; and the two may be separated from each other. If magnesium carbonate in powder be cautiously added to gastric juice or to an infusion of calves' stomach a copious precipitate is formed. If the addition of magnesium carbonate be stopped as soon as any further precipitation ceases to be caused by it, and the mixture be allowed to stand, the clear fluid left above the precipitate will be found to curdle milk readily, but even when acidified to have no peptic action on proteids, shewing that the precipitate caused by the addition of the magnesium carbonate has carried down all the pepsin but left behind at least a good deal of the 'curdling' or rennet-ferment.

It might be thought that the rennet-ferment, *rennin* we may call it, acted by inducing a fermentation in the sugar of milk, giving rise to lactic acid which precipitated the casein by virtue of its being an acid. But this view is disproved by the following facts which shew that the ferment produces its curdling effect by acting directly on the natural casein itself. Casein may be precipitated unchanged, that is capable of redissolving in water (the presence of calcic phosphate being assumed) by saturating milk with neutral saline bodies (such as sodium chloride or magnesium sulphate); and by being precipitated and redissolved more than once may be obtained largely free from fat and wholly free from milk-sugar. Such solutions of isolated casein freed from milk-sugar may be made to curdle like natural milk by the addition of rennin, shewing that the milk-sugar has nothing to do with the matter. Moreover the precipitate thrown down from milk by dilute acids, lactic acid included, is itself unaltered or very slightly altered casein not curd, and with care may be so prepared as to be redissolved into solutions which curdle with rennin, like solutions of casein prepared by means of neutral salts.

When isolated casein is curdled by means of rennin two proteids, it is stated, make their appearance, one which is soluble and allied to albumin, and another, which is insoluble and forms the curd. Curdling therefore according to this result appears to be the splitting up by a ferment of a more complex body; and it is interesting to observe, as perhaps throwing light on the somewhat analogous formation of fibrin, that this curdling action will not take place if calcic phosphate be wholly absent from the mixture. The calcic phosphate appears to play a peculiar part in determining the insolubility of the curd, for there is evidence that in the absence of calcic phosphate the ferment has power to attack the casein and split it up, but that both products remain in solution; if calcic phosphate be present, the one, viz. the curd[1], becomes insoluble.

Rennin is abundant in the gastric juice and in the gastric mucous membrane of ruminants, but is also found in the gastric juice of other animals, and either it, or what we shall presently have occasion to speak of as the antecedent of the ferment or *zymogen* is present also in the mucous membrane of the stomach of most animals. A very similar if not identical ferment has also been found in many plants.

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[1] It might be useful, in order to distinguish the curd from the natural soluble casein, to call the former *tyrein* (τυρὸς, cheese), and so reserve the name of casein for the latter.

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SEC. 2. THE STRUCTURE OF THE SALIVARY GLANDS, THE GASTRIC MUCOUS MEMBRANE, THE PANCREAS, AND THE ŒSOPHAGUS.

§ 208. Before we study the nature of the processes by which the stomach and the salivary glands are able to secrete the gastric juice and saliva, whose remarkable properties we have just described, it will be desirable to say a few words on the structure of both the above organs.

Throughout the greater part of its length, from the cardiac end of the œsophagus to near the anus, the alimentary canal is constructed on a certain general plan. This part of the alimentary canal is formed out of the mid-gut of the embryo, and the epithelium which lines it is of hypoblastic origin. The mouth and the anus have a different origin; they are formed by involutions of the external skin, the epithelium of which is of epiblastic origin; and the plan of structure of the mouth and terminal portion of the rectum is in some respects different from that of the rest of the alimentary canal. The transition from the epiblastic to the hypoblastic canal occurs in the rectum at the anus, but at the other end is at some distance from the mouth close to the junction of the œsophagus with the stomach.

The plan of structure of the hypoblastic portion of the canal is somewhat as follows.

A single layer of cylindrical, columnar, cubical or spheroidal "protoplasmic" cells, that is to say cells which are not transformed into flattened scales, forms the immediate lining of the cavity. The cells rest on a connective tissue basis, which is fine, delicate and often of a peculiar nature immediately under the epithelium, but becomes more open, loose and coarse at some little distance from the cells. This connective tissue basis is richly provided with blood vessels and lymphatics, and also contains a certain number of nerves. The blood vessels reach up to, and fine capillary networks are especially abundant immediately beneath, the bases of the cells, but none pass between the cells themselves;

the whole of the epithelium is extra-vascular. The connective tissue where it touches the cells forms a more or less continuous sheet; this is often spoken of as the basement membrane and may be regarded as the demarcation between the extra-vascular epithelium and the vascular connective tissue basis. The two together, the epithelium and the connective tissue basis, form what is known as the *mucous membrane.*

At the bases of the cylindrical cells, wedged in between them and the basement membrane, may be seen, in certain situations distinctly, in other situations less distinctly, small cells, that is to say cells the body of which is small relatively to the nucleus. These are supposed to be young cells, held in reserve to replace any of the larger cylindrical cells which may from time to time disappear; if so the epithelium does not strictly consist always of a single layer, though practically it may be so regarded.

Outside the mucous membrane or mucous coat is placed the thick *muscular coat.* This consists of two layers of plain muscular fibres, an inner thicker layer, in which the fibres and bundles of fibres are disposed circularly round the lumen of the alimentary canal, and an outer thinner one in which the fibres are disposed longitudinally. The bundles and sheets of fibres (see § 89) are bound together by connective tissue carrying blood vessels, lymphatics and nerves, and a thin sheet of connective tissue more or less distinctly separates the thicker inner circular muscular coat from the thinner outer longitudinal muscular coat.

The lower or outer part of the mucous membrane where it becomes attached to the muscular coat is formed of very loose connective tissue, the interspaces of the bundles being large and open. This is spoken of as the *submucous tissue* or *submucous coat.* It is so loose that the mucous coat can easily move over the muscular coat, and along it the one can easily be torn away from the other, more easily in some parts of the canal than in others. It carries the larger arteries and veins, whose smaller branches and capillaries pass into and from the mucous membrane. Lying in the mucous membrane at some little distance from the epithelium is found a thin layer of plain muscular fibres, called the *tunica muscularis mucosæ.* It is more conspicuous in some situations than in others, and when complete consists of an inner single layer of fibres disposed circularly and an outer single layer of fibres disposed longitudinally. The connective tissue on the inside of the muscularis mucosæ, between it and the epithelium, is generally of a somewhat different character from that outside the muscularis mucosæ, and many places is of the kind called *adenoid* or *reticular* tissue; of this we shall hereafter have to speak.

Lastly, from the stomach to the rectum the muscular coat of the alimentary canal is covered by the visceral layer of the peritoneum. This consists of a single layer of polygonal flattened nucleated epithelioid cells (belonging in reality as we shall see to the lymphatic system) resting on a thin connective tissue basis which separates them from the longitudinal muscular coat.

The general plan of structure of the alimentary canal then, in its hypoblastic portion, is a compact muscular coat separated by a loose more or less moveable submucous coat from a fairly compact mucous coat. The mucous coat consists of a vascular connective tissue basis, in which is embedded a thin special muscular sheet, and of a single layer of special hypoblastic epithelial cells. The muscular coat consists of a thick inner circular and a thin outer longitudinal layer of plain muscular fibres; and the whole is covered with an epithelioid peritoneal layer.

§ **209**. *Glands.* The surface of the mucous membrane however is not even and unbroken. It dips down at intervals, that is to say it is involuted to form pockets or depressions sunk into the underlying connective tissue and differing in size and form in different parts of the alimentary canal. Such an involution is called a *gland.* The most simple kind of gland is a cylindrical depression with a blind end, somewhat of the form of a test-tube, lined with a single layer of epithelium cells, continuous at the mouth of the gland with the rest of the epithelium of the mucous membrane. The wall of the gland outside the epithelium is supplied by the connective tissue of the mucous membrane, which generally forms a distinct basement membrane, and is generally also richly supplied with capillary blood vessels. Hence when two such glands lie side by side, a certain quantity of connective tissue carrying blood vessels runs up between them to reach the epithelial cells which cover the surface of the mucous membrane between their mouths. Such a simple tubular gland may have the same diameter throughout, or may vary in diameter at different distances from the mouth, and the epithelium lining it may be of the same character throughout and similar to that on the surfaces between the mouths of the glands; very frequently however at the lower part of the gland the epithelium is modified and takes on certain special characters which we shall speak of presently as those of a 'secreting' epithelium. When this occurs the upper part of the gland, where the epithelium is not so modified, is often spoken of as 'the duct' of the gland.

Very frequently the gland is not simple but branched, and the branching may be slight or excessive. Such branched glands, especially those in which the branching is considerable, are called *compound* glands; and in these there is always a very marked distinction between the terminal portions of the several branchings where the epithelial cells have secreting characters, and the proximal portions or ducts where the cells have not these secreting characters. In such a compound gland a tubular main duct (whose mouth opens into the interior of the alimentary canal, and whose epithelial lining is continuous with the general epithelial lining of the canal) divides, dichotomously or otherwise, into secondary ducts, which again divide into smaller ducts, and this division may be repeated again and again; ultimately however each duct ends in a part in which the epithelium takes on secreting characters, and such terminal portions of ducts which are generally wider, more swollen as it were, than the ducts leading to them and not infrequently flask-shaped are spoken of as *alveoli.* These alveoli, especially when flask-shaped, bear a certain, though by no means close, resemblance to the individual berries on a bunch of grapes, the ducts being the branching stalks; hence these compound glands are spoken of as "racemose." Sometimes the gland in dividing spreads out loosely over a wide surface, that is to say, is 'diffuse'; sometimes the ducts and alveoli with all the connective tissue, blood vessels, &c., belonging to them are bound up tightly into a more or less globular mass, that is to say, form a 'compact' gland.

Glands in fact vary widely in size, form and complexity, but they all have the one feature in common that they, being involutions of the mucous membrane, consist of a wall of vascular connective tissue lined by epithelium, and in the majority of glands there is a distinction in the characters of the epithelium between a terminal secreting portion and a proximal conducting portion.

Where, as in the stomach and intestine, a number of comparatively simple glands are closely packed together side by side, the whole mucous membrane acquires proportionately increased thickness; instead of being an attenuated sheet formed of a single layer of cells on a thin connective tissue basis it becomes a mass whose thickness is determined by the length of the glands.

It may be added that generally but not always the gland in its whole length lies above or outside the muscularis mucosæ, so that when a vertical section is made of a mucous membrane the muscularis mucosæ is seen running in an even line at some little distance below the thick layer which is presented by the longitudinal sections of the glands.

Bearing in mind these general characters of the alimentary canal and its glands we may now proceed to study some of its special characters, and it will be convenient to begin with the structure of the stomach.

Structure of the Stomach.

§ **210**. The stomach in its structure follows the general plan just described, and consists of a muscular coat and a mucous membrane separated from each other by loose submucous connective tissue. The muscular coat, which has considerable thickness, consists of an outer somewhat thick longitudinal coat and an inner still thicker circular coat, the innermost bundles of which take an oblique direction and form a more or less distinct thin oblique layer. As we shall see the movements of the stomach are more extensive and complex than those of the rest of the alimentary canal. Towards the pyloric end, in what is sometimes called the *antrum pylori*, the circular layer increases in thickness, and at the pylorus is developed into a thick ring called the sphincter of the pylorus; a less marked circular sphincter is also present at the cardiac orifice.

The size of the cavity of the stomach varies from time to time according to the bulk of contents present, and the condition of the muscular fibres. When the stomach is empty, the muscular fibres are in a state of tonic contraction, and the cavity is small; when the stomach is full, the muscular fibres though carrying out as we shall see more or less rhythmical movements are as a whole relaxed and extended, so that the cavity is large. The mucous membrane in its natural condition so to speak is of such a size that it forms a smooth even lining to the muscular coat when this is extended and relaxed and the cavity of the stomach distended. Hence when the stomach is empty, and the muscular coat contracted, the mucous membrane is thrown into folds or *rugæ*, which on account of the preponderance of the circular muscular coat take a longitudinal course, the loose submucous tissue allowing this movement of the mucous over the muscular coat.

The mucous membrane is relatively very thick, the thickness being due to the fact that the membrane over its whole extent is thickly studded with glands; it may in fact be said to be almost wholly composed of a number of short comparatively "simple" glands placed vertically side by side and bound together by just as much connective tissue as serves to carry the blood vessels and lymphatics. These glands vary in size, shape and character in different parts of the stomach, and the stomachs of different animals present in these respects very considerable differences; but, for present purposes, we may consider them as of two kinds, the glands at the cardiac end of the stomach or "cardiac glands" and the glands at the pyloric end, or "pyloric glands."

§ **211**. *Cardiac glands.* These are tubular glands, about ·5 mm. to 2 mm. in length by 50 μ to 100 μ in width, whose course is not wholly straight but wavy or gently tortuous, and frequently curved or bent at the blind end. Some are simple or unbranched, but others divide into two, three or even more tubes. They are packed together side by side in a vertical position so closely that in sections of hardened and prepared stomachs in which the blood vessels are for the most part emptied of blood and the lymph spaces of lymph, each gland seems to be separated from its neighbours by nothing more than an extremely thin sheet of connective tissue seen in sections as almost a mere line. In the living stomach when the numerous blood vessels in this connective tissue are filled with blood, and the lymph spaces are distended with lymph, the glands are separated from each other by a considerable space equal probably to about their own diameter.

The outline of each gland is defined by a distinct basement membrane which appears to be formed by a number of flat transparent connective tissue corpuscles fused together into a sheet; in a section of a gland, longitudinal or transverse, some of the nuclei belonging to the constituent cells may be seen embedded as it were in the basement membrane.

Each gland may be divided into a 'mouth,' by which it opens into the cavity of the stomach, and which reaches about a third or a quarter down the length of the gland, and into a 'body' which forms the rest of the gland, the junction of the two being called the 'neck.' These two parts differ fundamentally in structure.

The mouth has a wide open lumen and is lined with a single layer of long slender conical cells called 'mucous cells.' The lower two-thirds of each mucous cell, including the pointed or blunt or sometimes slightly branched end resting on the underlying basement membrane, is composed of ordinary granular looking protoplasm, staining with the ordinary staining reagents, embedded in the lower part of which is a small oval nucleus placed vertically.

The upper third is more clear and transparent, does not stain readily and differs in appearance at different times. At one time this part of the cell is occupied by mucus; at another time the mucus has been discharged by a rupture of the outer face or lid of the cell, leaving a small cup-shaped cavity (containing fluid and a remnant of mucus) the fairly distinct walls of which are continuous with the protoplasmic lower two-thirds of the cell. We shall shortly have to discuss more fully the nature of mucous cells in connection with the salivary glands, and may here simply say that in the upper third of the cell, the cell-substance of the cell, except for a portion which remains as the cell wall of this part of the cell, is transformed into mucus, and that the mucus so formed is sooner or later discharged from the cell, its place being in time occupied by new cell-substance which again in turn is converted into mucus.

These mucous cells not only line the mouths of the glands, becoming shorter where the mouth joins the neck, but also cover the ridges between the glands and so form the immediate lining of the interior of the stomach. The free surface or lid of each cell is more or less hexagonal or polygonal in outline, and in sections of hardened stomach the hardened cell-walls of the tops of the cells give rise to the appearance of a mosaic of hexagonal or polygonal areas where the section presents a number of these cells seen on end.

Lying between the bases of the mucous cells (which from the conical form of the cells diverge from each other) above the basement membrane may be seen in vertical sections a certain number of small cells, each consisting of a nucleus surrounded by a cell-body, which though small stains deeply and hence becomes conspicuous in stained sections. These as we previously said have been regarded as young reserve cells which will upon the destruction of any of the mucous cells grow up to take their place.

§ **212**. The body of the gland is not only in itself distinctly less in diameter than the mouth (so that a larger amount of vascular connective tissue lies between the bodies than between the mouths), but has a much narrower, indeed very narrow and tortuous lumen, and is lined by cells of a wholly different character. These are of two kinds.

Throughout its whole length below the mouth the gland is lined continuously with a single layer of polyhedral or cubical or at times conical cells, the outlines of which are remarkably indistinct. The cell-body of each of these, which contains a spherical nucleus placed near the centre of the cell but more outside towards the basement membrane, varies, as we shall see later on, very much in appearance according to what has been taking place in the stomach, and to the mode of preparation. In sections of a stomach hardened and prepared in an ordinary way the cell-bodies frequently present a "faintly granular" appearance. Cells of this kind are spoken of from their position as *central* cells, or sometimes, for reasons which we shall see presently, as *chief* cells.

The cells of the other kind do not form a continuous layer but are scattered along the length of the body of the gland, being most numerous (but smaller) in the region of the neck, and less frequent (but larger) at the bottom or fundus of the gland. They are moreover in the lower part of the gland and indeed over the greater part placed outside the central cells, being wedged in between these and the basement membrane and frequently causing the latter to bulge out; they therefore in most cases do not abut on the lumen of the gland and their only direct connection with the lumen is through spaces between the central cells. In the neck of the gland they may however bound the lumen. Each cell is ovoid in form with an outline which, in contrast to that of the central cells, is sharp and well defined, and possesses an ovoid nucleus placed in the middle of a cell-body which like that of the central cell varies in appearance according to circumstances, but which in a section of stomach hardened and prepared in an ordinary way is frequently 'coarsely' granular. Cells of this kind are called from their position *parietal* cells or, from their shape, *ovoid* cells. Even the smaller of them are larger than the central cells.

A characteristic 'gastric gland' then of the cardiac region of the stomach is a tubular depression often straight and simple, but at times bifurcating towards the lower part or otherwise dividing, the ends frequently curling. Each depression consists of a mouth, with a broad lumen lined by slender mucous cells, a neck in which the mucous cells suddenly change to central cells with numerous ovoid cells lying among them, and in which the lumen becomes narrowed and tortuous, and a body ending in a blind fundus, with the lumen still narrow winding between the central cells outside which are placed ovoid cells less numerous than in the neck. Such glands placed side by side form the thickness of the mucous membrane, and below them at a short distance runs in a tolerably even line the thin muscularis mucosæ with its single inner circular and outer longitudinal layers of plain muscular fibres.

§ **213**. The space between the level of the bottom of the glands and the muscularis mucosæ as well as the vertical spaces between the glands, that is all the space between the much folded basement membrane above and the muscularis mucosæ below is occupied by delicate connective tissue the meshwork of which, formed of thin narrow sheets or laminæ rather than of fibres or bundles, becomes especially close set immediately under the basement membrane. In the spaces of the meshwork a certain number of lymph corpuscles or leucocytes may be seen. Small arteries passing upwards from the submucosa through the muscularis mucosæ break up into capillaries encircling the glands in the form of plexuses which are especially close set at the summits of the spaces between the glands, that is to say at the places where the connective tissue lies nearest to the interior of the stomach. Small veins springing from these capillaries, especially from those last named, running downwards pierce the muscularis mucosæ and form the larger veins in the submucous coat. Lymphatic vessels and structures called lymphatic 'glands' are present in the mucous coat, but of these we shall speak later on.

§ **214**. *Pyloric glands.* At the pyloric end of the stomach the glands are less closely packed than at the cardiac end, and differ from the cardiac glands in size, shape and structure. A typical pyloric gland possesses a mouth which is much longer and generally broader with a wider lumen than the mouth of a cardiac gland, though the walls are lined with mucous cells like those of the cardiac end. The body of the gland instead of being as in the cardiac gland often tubular and unbranched, frequently divides into two or more branches close to the neck, and these branches which are relatively shorter than the body of a cardiac gland and have a much wider lumen, may again subdivide so that the whole gland is most distinctly branched. The whole body with all its branches from the mouth to the several blind ends is lined throughout with one kind of cell only, which is very similar to the central cell of a pyloric gland, inasmuch as it is a polyhedral or short columnar cell with indistinct outlines, a spherical nucleus, and a cell-body which in a specimen prepared in the ordinary way is faintly granular. The 'ovoid' cell so characteristic of the cardiac gland is absent. The arrangement of the connective tissue with its blood vessels and lymphatics and of the muscularis mucosæ is much the same as at the cardiac end.

Thus the cardiac end of the stomach contains glands which are tubular and often simple, which have a very narrow lumen, and which possess central and ovoid cells, while the pyloric end contains glands which are branched, which have a relatively deep mouth and wide lumen, and which possess one kind of cells only, central cells or cells very like these. In the middle region of the stomach the one kind of gland gradually merges into the other; in passing from the cardia to the pylorus the ovoid cells become less numerous and at last disappear, the mouth becomes longer, the lumen wider, and the body of the gland becomes more and more branched.

The above supplies a general description of the gastric glands but these vary in minor characters and to a certain extent in distribution in different animals; and as we shall presently see in all cases, the glands vary in condition and so in appearances according as digestion is or has been going on in the stomach.

The Salivary Glands.

§ **215**. The structural differences between the 'mucous' cells lining the mouth and the 'central' and 'ovoid' cells lining the body of a gastric gland lead us to infer that the former differ from the latter in function; and we have other evidence that this is so, that it is the central and ovoid cells which actually secrete the gastric juice, and that as far as the gastric juice is concerned, the mouths of the glands serve chiefly (though the mucous cells have a purpose of their own) to conduct to the interior of the stomach the juice secreted by the body of the gland. We may therefore speak of the body as the secreting portion and the mouth as the 'duct' of the gland.

This distinction between a secreting portion and a conducting portion, more or less obvious as we have said in most glands, is especially striking in the case of the salivary glands. These are involutions of the (epiblastic) mucous membrane of the mouth as the gastric glands are involutions of the (hypoblastic) mucous membrane of the stomach; but instead of being comparatively simple they are exceedingly branched racemose glands, and the secreting portion of the gland is removed to a great distance from the epithelium of the mouth so that the conducting portion is of very great length. Moreover, not only the epithelium lining the secreting portion but also that lining the conducting portion differs so completely from the epiblastic epithelium lining the mouth that we may study the structure of the gland quite apart from the structure of the lining of the mouth, whose sensory functions, in the way of taste for instance, are so much more important than its digestive functions that we may reserve the study of its features until we come to deal with the senses.

A salivary gland such as the submaxillary consists of a long main duct which pursues an undivided course backwards for several centimetres from its opening into the cavity of the mouth until it reaches the body of the gland, when it rapidly divides and subdivides into a number of smaller ducts. Each of the ultimate divisions of the duct at last ends in a 'secreting' portion, which is lined by a 'secreting' epithelium different in character from the epithelium lining the ducts. Such a terminal secreting portion is called an *alveolus.* Sometimes a duct terminates in a single alveolus, which then appears as a swollen or somewhat flask-shaped termination of the duct distinguished from the duct by the size and character of its cells and by the narrowness of its lumen; but more commonly a duct ends in several alveoli, which then appear as a number of short curved somewhat swollen tubes, branching off from the end of the duct. All the ducts and the alveoli in which they end are bound up by connective tissue, carrying blood vessels, nerves and lymphatics, into a compact, rounded but somewhat lobulated mass, the gland proper. Each alveolus, or each group of alveoli, and the small duct of which it forms the blind end is surrounded and separated from its neighbours by a certain amount of connective tissue. A number of alveoli with the ducts leading to them are bound together into a *lobule* by a rather larger amount of connective tissue. Groups of these smaller lobules are bound together by connective tissue and enveloped by a more distinct coat of that tissue, and thus form larger or primary lobules; and these larger lobules are bound up to form the gland itself by a quantity of connective tissue, which also forms a wrapping or sheath for the whole gland. Hence a thin section taken through the gland is seen, when examined under a low power, to be divided by septa of connective tissue (continuous with the sheath of the gland, and carrying blood vessels, &c.), into irregular areas, which are generally angular from compression. These areas are sections of the primary lobules, and each may be seen to be similarly but less distinctly subdivided into similar smaller areas, the smaller lobules. Each of these smaller lobules will in turn be seen to be for the most part made up of rounded bodies varying somewhat in size and shape but on the whole very much alike, bound together by a small amount of connective tissue; these are the alveoli which, being disposed in various directions and being frequently more or less curved, are cut in various planes by the section. Where the section cuts the alveolus transversely the outline of the alveolus is circular, where obliquely the outline is more elliptical; a section moreover may pass through the mere tip or side of the alveolus and so miss the lumen altogether; and indeed many varied appearances may be presented. Among these alveoli are seen other bodies of a somewhat different aspect, circular, elliptical or cylindrical in outline, or hour-glass-shaped, or even irregular in form. These are the small tubular ducts cut in various planes. Sections of the larger ducts of various size may also be seen in the septa between the lobules. Even with quite a low power it is easy to distinguish between the alveoli or secreting elements and the ducts, and when we come to examine them more closely we find that they differ markedly in structure. Moreover, when we examine the three glands, parotid, submaxillary and sublingual, and especially when we employ for the purpose different kinds of animals, we find that, while the ducts have nearly the same structure in all cases, two kinds of alveoli may be distinguished differing from each other in the characters of the cells lining them. In the one case the cells, for reasons which will presently appear, are called *mucous cells*, in the other *serous cells*, or perhaps better *albuminous cells*. In one gland all the alveoli may be lined with mucous cells, in which case it is called a 'mucous gland,' or with albuminous cells, in which case it is called an 'albuminous gland,' or some alveoli may be 'mucous' and others 'albuminous,' the gland being a mixed one; and this distinction between mucous and albuminous obtains also in glands of the mucous membrane which are not distinctly salivary, for instance in the small 'buccal' glands of the mouth, and in the glands of the pulmonary passages and of other structures.

§ **216**. *Mucous glands.* The submaxillary gland of the dog is a fairly typical mucous gland. The alveoli of this gland vary a good deal in diameter, but are on an average about 35 μ. The outline of each alveolus is defined by a distinct basement membrane formed of a number of flattened connective tissue corpuscles fused together into a sheet; in a section the long oval nuclei of the constituent cells may be seen here and there imbedded, as it were, in the membrane. Outside the basement membrane lie, as elsewhere in a mucous membrane, the lymph spaces of the fine connective tissue.

The space defined by the basement membrane is nearly wholly filled, a very small central lumen only being left, by cells arranged for the most part in a single layer. The cells are large relatively to the alveolus, so that in a transverse section of an alveolus, about 5 or 6 cells will be seen. Each cell is more or less spherical or rather conical in form, with its broader base, which is sometimes irregular in outline, resting on the basement membrane and the narrower apex abutting on the lumen. The characters of the cell differ according to the condition of the gland. If the gland has, previous to its preparation for examination, not been actively secreting, the cells have certain characters and may be spoken of as 'loaded' or 'charged.' If the gland has been actively secreting, these characters are replaced by others, and the cells may be spoken of as 'unloaded,' 'discharged.' In the 'loaded,' or as it is often called the 'resting' phase, the cell, in hardened specimens, is as a whole transparent, and stains very slightly with the ordinary staining reagents. The nucleus, which in hardened specimens appears disc-shaped and sometimes curved or bent, but in the fresh living cell is seen to be spherical, lies at the base of the cell not far from the basement membrane. Around the nucleus is gathered a small quantity of ordinary protoplasmic cell-substance, staining readily with the usual dyes; the rest of the cell-body consists of a transparent material, which does not stain readily, and which occupies the spaces or meshes of a very delicate meshwork continuous apparently with the staining protoplasmic cell-substance around the nucleus, and with a thin sheet of similar material forming the wall of the cell. This transparent material is either mucin, which we have seen to be a conspicuous constituent of submaxillary saliva (in the dog) or a substance which can be easily converted into actual mucin, that is to say an antecedent of mucin; hence the name 'mucous cell.' A resting or loaded mucous cell then consists largely of mucin (or its antecedent) lodged in the meshes of the protoplasmic cell-substance which over the greater part of the cell exists, in a hardened gland at any rate, as a delicate meshwork or reticulum, but is gathered into a compact mass in a small area immediately around the nucleus.

In many alveoli, a more or less triangular space left between the diverging bases of two of the mucous cells and the basement membrane may be seen to be occupied by one or by two or more peculiar small cells. These on examination are found to be irregular in form but often half-moon shaped, and are hence called *demilune* cells. Each consists of deeply staining cell-substance with a spherical nucleus. From their size, and their staining deeply, as well as from their position, these demilune cells contrast strongly with the mucous cells.

In the 'discharged,' or as it is often called the 'active' phase, the mucous cell has a different appearance, especially if the activity of the gland has been great. The cell is now smaller, and thus gives rise to a more distinct lumen in the alveolus, a larger portion of the cell stains, especially on the outer side, and sometimes the whole cell stains; the nucleus, now spherical even in hardened specimens, occupies a more central position. The transparent, non-staining mucin has in large part or wholly disappeared, its place has been taken by ordinary staining protoplasmic cell-substance, and the distinction between the demilune cells and the proper cells of the alveolus is much less distinct. We shall presently have to discuss the nature and meaning of this change from the loaded to the discharged cell.

§ **217**. A small duct of the submaxillary gland, even when cut transversely in the section so as to present like many alveoli a circular outline, has an appearance very different from that of an alveolus. The duct is lined by a single layer of epithelium, but these are slender, narrow, columnar cells leaving in the centre a relatively wide lumen, and the outside of the duct is not so sharply defined by a conspicuous basement membrane as is the case in an alveolus. Each cell, which bears an oval nucleus placed vertically in the cell at about the middle but rather nearer the base, consists of a protoplasmic cell-substance which on the inner side of the nucleus towards the lumen has no special features, but on the outside, towards the basement membrane or connective tissue basis, has frequently a longitudinal striation as if made up of a number of rods or narrow prisms placed side by side.

The larger ducts running between the lobules differ from such a small intralobular duct chiefly in the greater thickness of the connective tissue basis, which in these is developed into a distinct coat containing in the case of the larger branches and the main duct plain muscular fibres. In the main duct and its chief branches the single layer of columnar cells is replaced by two or three layers of cubical, or sometimes flattened cells not marked with the striation spoken of above. When a small intralobular duct is about to end in an alveolus or a group of alveoli it becomes narrowed, the cells lose their striation, from being slender and cylindrical in form become short cubical, and at the very end of the duct change into flat spindle-shaped plates, the transition from which to the characteristic cells of the alveolus is in the case of most animals quite abrupt. Such a modified terminal portion of a duct is sometimes spoken of as a "ductule."

§ **218**. *Albuminous glands.* These differ from the mucous glands in the constitution of the cells lining the alveoli, but the structure of the ducts and the general arrangements of the gland are the same in both; indeed, as we have already said, in the same gland some alveoli may be albuminous and others mucous.

In an albuminous alveolus the cells are rather smaller than those in a loaded mucous gland, and their outlines are rather more angular. In each cell the nucleus, which is spherical, is placed near the centre of the cell but rather nearer the basement membrane, and the cell-substance, which has the general appearance, in an ordinary preparation, of somewhat densely granular protoplasm, stains readily and uniformly all over. No cells corresponding to the demilunes of a mucous alveolus are present. In fact an albuminous cell does not at first sight appear to differ markedly from a discharged mucous cell, and does not shew the same marked differences between a loaded and a discharged condition as does a mucous cell. There are however differences between the loaded and the discharged albuminous cell, but to these we shall return presently.

The parotid gland of man and indeed of all mammals is a wholly albuminous gland, though in the dog a few cells are mucous; the submaxillary of man is on the whole a mucous gland but some lobules in it are albuminous; the submaxillary of the rabbit is an albuminous gland. The sublingual may perhaps in all mammals be regarded as a mucous gland, though it differs in several respects from other mucous glands; the cells lining the ducts are much shorter and less distinctly striated, the alveoli are more obviously branched tubules, and the cells of some alveoli contain no mucin.

The small buccal glands which lie in the substance of the mucous membrane of the mouth, and whose secretion contributes to "mixed" saliva, are formed, on a small scale, after the plan of a salivary gland, that is to say, they are composed of a duct (or ducts) and alveoli which in structure are similar to those of a salivary gland. They further resemble the salivary glands in that some of them are 'albuminous' and some 'mucous.'

§ **219**. The salivary glands have each of them a special nervous supply of which we shall speak in detail in the following section, and will here simply say that the fibres passing into the glands are both medullated and non-medullated fibres, and that the terminations of the fibres have not been as yet exactly made out; for, though it has been maintained by some observers that some of the nerve-fibres end in the secreting cells, this has not been satisfactorily proved. Numerous nerve-cells may be seen scattered along the nerve-fibres where they pass into the gland at the 'hilus' whence the main duct issues.

Of the nervous supply of the stomach, derived partly from both vagi nerves, and partly from the solar plexus, we shall also have to speak later on, we may here simply say that the fibres end for the most part in a peculiar plexus between the circular and longitudinal muscular layers, and in another peculiar plexus in the submucous coat, the two plexuses corresponding to what we shall describe in the small intestine as the plexus of Auerbach and the plexus of Meissner.

The Pancreas.

§ **220.** The structure of the pancreas is so similar to that of a salivary gland that though we shall not deal with the properties and characters of the pancreatic juice until later on, it will be convenient to consider the histology of the gland now.

Whether as in man, in the dog and in most other animals it forms a compact mass, or as in the rabbit is spread out into a thin sheet, the pancreas is in all cases a compound racemose gland, consisting of ducts and alveoli arranged in lobes and lobules. In man the smaller ducts join one main duct, which running lengthwise through the gland pierces the coats of the duodenum in company with, and opens into the interior of the intestine by an orifice common to it and to the bile duct. Not infrequently a second but smaller main duct coming from the lower part of the head of the gland joins the intestine lower down; in the dog such a second duct is a usual occurrence. In the rabbit the main duct does not join the intestine with the bile duct, but at a considerable distance, several centimetres, lower down, so that in this animal the bile and pancreatic juice are not poured together into the intestine, but the food is for a distance exposed to the action of the former before it meets with the latter.

The structure of the ducts is, in all essential points, similar to that of the ducts of a salivary gland, save that the striation of the epithelial cells is less distinct. As in the case of the salivary gland, the ductule, or narrow terminal portion of the duct, just as it joins the alveoli is lined by flat spindle-shaped cells.

The alveoli also are similar to those of a salivary gland save perhaps that they are relatively longer and more tubular; the lumen in all cases is very narrow. As compared with a salivary gland the alveoli are relatively more numerous than the ducts, so that in a section of the gland relatively fewer ducts are seen cut across. Each alveolus is lined with one kind of cell only, which is much more similar to an albuminous than to a mucous cell; there are no demilune cells. The more minute features of the alveolus differ according as the gland has been 'resting' and so is 'loaded,' or has been 'active' and so is 'discharged.' The cells lining the alveolus are more or less polyhedral in form, and each cell consists of a clear transparent cell-body, in which occur a number of refractive discrete "granules;" a spherical nucleus lies at about the outer third of the cell. In a 'loaded' cell these granules are very abundant, and reach from the narrow, inconspicuous lumen to near the outer margin of the cell, so as to leave only a narrow clear transparent zone immediately bordering on the basement membrane; the cell-substance is so thickly studded with these 'granules' that the nucleus is completely hidden, and the greater part of the cell appears quite dark. In a 'discharged' cell these granules are far less numerous, and are largely confined to the inner part of the cell abutting on the lumen, so that there is established a clear distinction between a narrow inner "granular" zone and a clear transparent outer zone, free or nearly free from granules. The width of the granular zone varies in fact with the condition of the gland; when the gland has been very active the granular zone is very narrow, when moderately active, it is broader, and when the gland has been for some time wholly at rest and is therefore loaded, the granular zone may encroach on nearly the whole cell. But we shall have to return to these matters presently.

In the pancreas of the rabbit and some other animals groups of cells of a peculiar nature may be seen intercalated at intervals in the midst of the true glandular substance. These are rounded or polyhedral in form, and have a clear cell-substance with a relatively large nucleus; they do not form alveoli and they have no ducts. Each of these groups is supplied with blood vessels forming a capillary network more close set than elsewhere. The exact nature of these cells is at present a matter of doubt.

The pancreas is supplied with nerves coming from the solar plexus, and consisting partly of medullated and partly of non-medullated fibres. As in the case of the salivary glands nerve-cells are found in connection with the nerve-fibres as these pass into the gland.

The Structure of the Œsophagus.

§ **221**. In the general plan of its structure the œsophagus resembles the rest of the alimentary canal, for it consists of a mucous membrane, with a muscularis mucosæ and glands, a loose submucous coat, and a muscular coat comprising an inner circular and an outer longitudinal layer. But the epithelium, epiblastic in origin, is very different from that of the stomach or intestine, and both circular and longitudinal muscular layers are composed to a large extent not of unstriated but of striated fibres like those of the skeletal muscles.

In a vertical section of the œsophagus it will be seen that the epithelium is not arranged as a single layer of cells, but is several cells deep. The lower cells near the basement membrane, which is not very distinct, are cylindrical or spheroidal cells with granular 'protoplasmic' cell-substance, but those nearer the surface are more flattened, and the uppermost cells are mere flattened nucleated scales, the bodies of which are no longer protoplasmic but have become changed into a peculiar material. Such an epithelium is called a 'stratified' epithelium. A similar epithelium lines the greater part of the pharynx and the mouth, and is continuous with the corresponding epithelium of the skin or "epidermis" of which we shall have to speak later on. At the cardiac orifice there is a sudden transition from this stratified epithelium to the gastric epithelium previously described.

The looseness of the submucous coat permits the mucous membrane to be thrown into temporary longitudinal folds which disappear when the canal is distended. But besides this, the line of the basement membrane, of the connective tissue basis of epithelium, 'dermis' or 'corium' as the corresponding part of the skin is called, is raised up into a number of permanent conical elevations or *papillæ*, in which the connective tissue is especially fine and which are richly provided with blood vessels. The surface line of the epithelium does not follow the inequalities of the dermis produced by these papillæ, but remains fairly even. In the presence of these papillæ the mucous membrane of the œsophagus also resembles the skin, but in the latter structure the papillæ are more abundant and more regular in form and size.

The dermis, or connective tissue basis of the epithelium, is a network of fibres and fine bundles of connective tissue, with connective tissue corpuscles and a considerable number of fine elastic fibres; the number of leucocytes in the meshes of the network is relatively scanty. A few scattered masses of retiform or adenoid tissue, of which we shall speak later on, occur here and there.

The mucous membrane proper is defined from the underlying submucous tissue by a muscularis mucosæ of plain unstriated muscular fibres, lying at some distance from the epithelium. These muscular fibres are absent at the upper part of the œsophagus, appear lower down in isolated longitudinal bundles, and eventually form a distinct layer, which however is not so regular as in the rest of the alimentary canal, and consists of longitudinal fibres only, circular fibres being absent.

In man a few but in other animals a considerable number of small 'mucous' and 'albuminous' glands are found in the submucous tissue; their ducts, penetrating the muscularis mucosæ where present, open on to the surface of the mucous membrane. In man and mammalia these glands appear to serve only the purpose of keeping the internal surface of the œsophagus moist; but in some animals, as in the frog, in which the epithelium of the œsophagus is not the many layered stratified epithelium just described, but a single layer of columnar ciliated cells mixed with mucous cells, of the kind which we shall later on describe as 'goblet' cells, there is a large development of glands at the lower part of the œsophagus, and the cells of these glands manufacture pepsin.

As in other parts of the alimentary canal the submucous tissue carries the larger blood vessels whose smaller branches supply the mucous membrane; and lymphatics, beginning in the mucous membrane, form considerable plexuses in the submucous coat.

§ **222**. In man both the thicker inner circular and the outer thinner longitudinal muscular layer consist in the upper part of the œsophagus exclusively of bundles of striated fibres, which in their main characters are identical with ordinary fibres of skeletal muscles. At about the end of the upper third or sooner, bundles of plain unstriated fibres make their appearance among the bundles of striated fibres, and a little lower down the striated fibres disappear, so that, in the lower half or more of the tube, both circular and longitudinal layers are composed almost exclusively of plain unstriated fibres, a few stray bundles of striated muscle being found here and there. The relation of the striated and unstriated fibres differs however in different animals; in some the striated tissue reaches down nearly to the stomach.

Above, both longitudinal and circular layers merge into the inferior constrictor of the pharynx; below, the longitudinal bundles spread out in a radial fashion to join the corresponding longitudinal muscular coat of the stomach, and the circular fibres are also continuous with the circular and oblique layers of the stomach, more especially with the latter. Before the circular fibres thus spread out over the stomach, they undergo a somewhat increased development forming a sort of sphincter of the cardiac orifice.

Outside the longitudinal muscular coat of the œsophagus there is a considerable development of connective tissue forming what is sometimes spoken of as a fibrous sheath. In, or rather perhaps on, this sheath in the lower part of the œsophagus run the two vagi nerves, with the œsophageal plexus which is formed by branches running from the one to the other. In it also run the larger blood vessels.

§ **223**. It is obvious that the œsophagus is much more a muscular than a secreting structure, and further that a distinction is to be made between the upper part of the œsophagus where the muscular fibres are striated, and the lower part where they are unstriated. Corresponding more or less clearly to this distinction we find that though the whole œsophagus is supplied by nerve fibres from the trunk of the vagus (which however it must be remembered contains besides fibres of the vagus proper, fibres from the spinal accessory nerve and from other sources) the supply to the upper part takes a different course from the supply to the lower part. Thus in man the upper part is supplied by branches of the recurrent laryngeal nerve as it runs up between the trachea and œsophagus, while the lower part derives its nerve fibres from the œsophageal plexus formed by the two vagi. In various animals the supply of the upper part varies, coming in some cases chiefly from the pharyngeal branch of the vagus, and being in the rabbit a distinct branch of the vagus. In all cases however it would seem that the lower part of the œsophagus, the upper limit being placed higher or lower in different animals, is supplied from the œsophageal plexus. It may be remarked that the fibres in this plexus are for the most part non-medullated fibres, but we shall have to return to these nerves in speaking of the movements of the œsophagus.

SEC. 3. THE ACT OF SECRETION OF SALIVA AND GASTRIC JUICE AND THE NERVOUS MECHANISMS WHICH REGULATE IT.

§ **224**. The saliva and gastric juice whose properties we have studied, though so different from each other, are both drawn ultimately from one common source, the blood, and they are poured into the alimentary canal, not in a continuous flow, but intermittently as occasion may demand. The epithelium cells which supply them have their periods of rest and of activity, and the amount and quality of the fluids which these cells secrete are determined by the needs of the economy as the food passes along the canal. We have now to consider how the epithelium cell manufactures its special secretion out of the materials supplied to it by the blood, and how the cell is called into activity by the presence of food, it may be as in the case of saliva at some distance from itself, or by circumstances which do not bear directly on itself. In dealing with these matters in connection with the digestive juices, we shall have to enter at some length into the physiology of secretion in general.

The question which presents itself first is: By what mechanism is the activity of the secreting cells brought into play?

While fasting, a small quantity only of saliva is poured into the mouth; the buccal cavity is just moist and nothing more. When food is taken, or when any sapid or stimulating substance, or indeed a body of any kind, is introduced into the mouth, a flow is induced which may be very copious. Indeed the quantity secreted in ordinary life during 24 hours has been roughly calculated at as much as from 1 to 2 litres. An abundant secretion in the absence of food in the mouth may be called forth by an emotion, as when the mouth waters at the sight of food, or by a smell, or by events occurring in the stomach, as in some cases of nausea. Evidently in these instances some nervous mechanism is at work. In studying the action of this nervous mechanism, it will be of advantage to confine our attention at first to the submaxillary gland.

§ **225**. The submaxillary gland is supplied with two sets of nerves. These are represented in Fig. 62, which is a very diagrammatic rendering of the appearances presented when the submaxillary gland is prepared for an experiment in a dog, the animal being placed on its back and the gland exposed from the neck. The one set, and that the more important, belongs to the *chorda tympani* nerve (*ch.t''*). This is a small nerve, which branches off from the facial or seventh cranial nerve in the Fallopian canal before the nerve issues from the skull. Whether it really belongs to the facial proper has been doubted; in man the fibres which form it are either fibres coming not from the roots of the facial proper but from the *portio intermedia Wrisbergi*, or, according to some, fibres which though joining the facial in the Fallopian canal are ultimately derived from another (the fifth) cranial nerve. Leaving the facial nerve the chorda tympani passes through the tympanic cavity or drum of the ear (hence the name) and joins or rather runs in company (*ch.t'*) with the lingual or gustatory branch of the fifth nerve. Some of the fibres run on with the lingual right down to the tongue (these are not shewn in the figure), but many leave the lingual as a slender nerve (*ch.t*), which reaching Wharton's duct or duct of the submaxillary gland (*sm.d*) runs along the duct to the gland. As the nerve courses along the duct nerve cells make their appearance among the fibres, and these are especially abundant just after the duct enters the hilus of the gland. The fibres may be traced into the gland for some distance, but as we have said their ultimate ending has not yet been definitely made out. Along its whole course up to the gland, the fibres of the chorda are very fine medullated fibres, but they lose their medulla in the gland.

The other set of nerve-fibres reaches the gland along the small arteries of the gland. These are non-medullated fibres mixed with a few medullated fibres and may be traced back to the superior cervical ganglion. From thence they may be traced still further back down the cervical sympathetic to the spinal cord, following apparently the same tract as the vaso-constrictor fibres, treated of in § 166.

§ **226**. If a tube be placed in the duct, it is seen that when sapid substances are placed on the tongue, or the tongue is stimulated in any other way, or the lingual nerve is laid bare and stimulated with an interrupted current, a copious flow of saliva takes place. If the sympathetic be divided, stimulation of the tongue or lingual nerve still produces a flow. But if the small chorda nerve be divided, stimulation of the tongue or lingual nerve produces no flow.

Evidently the flow of saliva is a nervous reflex action, the lingual nerve serving as the channel for the afferent and the small chorda nerve for the efferent impulses. If the trunk of the lingual be divided above the point where the chorda leaves it, as at *n.l′*, Fig. 62, stimulation of the (front part of) tongue produces, under ordinary circumstances, no flow. This shews that the centre of the reflex action is higher up than the point of section; it lies in fact in the brain.

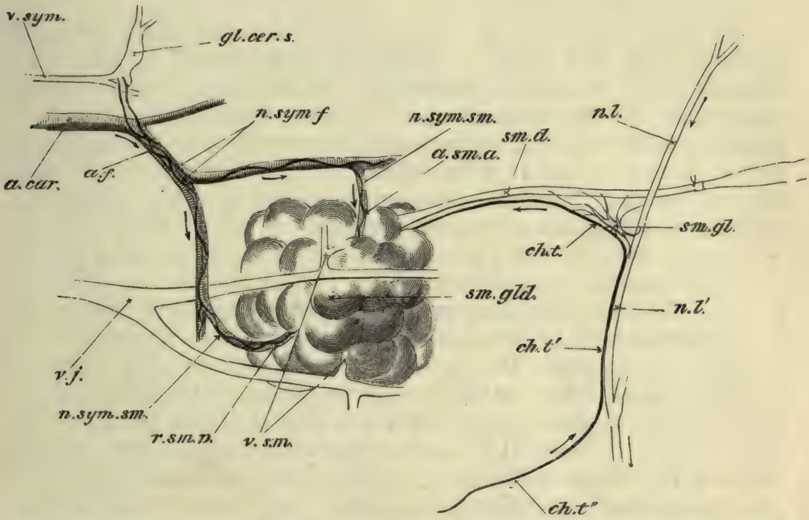

Fig. 62. Diagrammatic Representation of the Submaxillary Gland of the Dog with its Nerves and Blood Vessels.

(The dissection has been made on an animal lying on its back, but since all the parts shewn in the figure cannot be seen from any one point of view, the figure does not give the exact anatomical relations of the several structures.)

sm. gld. The submaxillary gland, into the duct (*sm. d.*) of which a cannula has been tied. The sublingual gland and duct are not shewn. *n. l.*, *n. l′.* The lingual branch of the fifth nerve, the part *n. l.* is going to the tongue. *ch. t.*, *ch. t′.*, *ch. t″.* The chorda tympani. The part *ch. t″.* is proceeding from the facial nerve; at *ch. t′.* it becomes conjoined with the lingual *n. l′* and afterwards diverging passes as *ch. t.* to the gland along the duct; the continuation of the nerve in company with the lingual *n. l.* is not shewn. *sm. gld.* The submaxillary ganglion with its several roots. *a. car.* The carotid artery, two small branches of which, *a. sm. a.* and *r. sm. p.*, pass to the anterior and posterior parts of the gland. *v. s.m.* The anterior and posterior veins from the gland, falling into *v. j.* the jugular vein. *v. sym.* The conjoined vagus and sympathetic trunks. *g. cer. s.* The upper cervical ganglion, two branches of which forming a plexus (*a. f.*) over the facial artery, are distributed (*n. sym. sm.*) along the two glandular arteries to the anterior and posterior portions of the gland.

The arrows indicate the direction taken by the nervous impulses during reflex stimulation of the gland. They ascend to the brain by the lingual and descend by the chorda tympani.

In the angle between the lingual and the chorda, where the latter leaves the former to pass to the gland, lies the small submaxillary ganglion (represented diagrammatically in Fig. 62 *sm. gl.*). This consists of small masses of nerve cells lying on the small bundles of nerve-fibres which spread out like a fan from the lingual and chorda tympani nerves (*ch. t.*) towards the ducts of the submaxillary and sublingual glands. It has been much debated whether this ganglion can act as a centre of reflex action in connection with the submaxillary gland, but no conclusive evidence that it does so act has as yet been shewn; it probably belongs in reality to the sublingual gland.

Stimulation of the glossopharyngeal is even more effectual than that of the lingual. Probably this indeed is the chief afferent nerve in ordinary secretion. Stimulation of the mucous membrane of the stomach (as by food introduced through a gastric fistula) or of the vagus may also produce a flow of saliva, as indeed may stimulation of the sciatic, and probably of many other afferent nerves. All these cases are instances of reflex action, the cerebro-spinal system acting as a centre. We may further define the centre as a part of the medulla oblongata, apparently not far removed from the vaso-motor centre. When the brain is removed down to the medulla oblongata, that organ being left intact, a flow of saliva may still be obtained by adequate stimulation of various afferent nerves; when the medulla is destroyed no such action is possible. And a flow of saliva may be produced by direct stimulation of the medulla itself. When a flow of saliva is excited by ideas, or by emotions, the nervous processes begin in the higher parts of the brain, and descend thence to the medulla before they give rise to distinctly efferent impulses; and it would appear that these higher parts of the brain are called into action when a flow of saliva is excited by distinct sensations of taste.

Considering then the flow of saliva as a reflex act the centre of which lies in the medulla oblongata, we may imagine the efferent impulses passing from that centre to the gland either by the chorda tympani or by the sympathetic nerve. Although it would perhaps be rash to say that in this relation the sympathetic nerve never acts as an efferent channel, as a matter of fact we have no satisfactory experimental evidence that it does so; and we may therefore state that, practically, the chorda tympani is the sole efferent nerve. Section of that nerve, either where the fibres pass from the lingual nerve and the submaxillary ganglion to the gland, or where it runs in the same sheath as the lingual, or in any part of its course from the main facial trunk to the lingual, puts an end, as far as we know, to the possibility of any flow being excited by stimuli applied to the sensory nerves, or to the sentient surfaces of the mouth or of other parts of the body.

The natural reflex act of secretion may be inhibited, like the reflex action of the vaso-motor nerves, at its centre. Thus when, as in the old rice ordeal, fear parches the mouth, it is probable that the afferent impulses caused by the presence of food in the mouth cease, through emotional inhibition of their reflex centre, to give rise to efferent impulses.

§ 227. In life, then, the flow of saliva is brought about by the advent to the gland along the chorda tympani of efferent impulses, started chiefly by reflex actions. The inquiry thus narrows itself to the question: In what manner do these efferent impulses cause the increase of flow?

If in a dog a tube be introduced into Wharton's duct, and the chorda be divided, the flow, if any be going on, is from the lack of efferent impulses arrested. On passing an interrupted current through the peripheral portion of the chorda, a copious secretion at once takes place, and the saliva begins to rise rapidly in the tube; a very short time after the application of the current the flow reaches a maximum which is maintained for some time, and then, if the current be long continued, gradually lessens. If the current be applied for a short time only, the secretion may last for some time after the current has been shut off. The saliva thus obtained is but slightly viscid, and under the microscope a very few salivary corpuscles, and, occasionally only, amorphous lumps of peculiar material, probably mucous in nature, are seen. If the gland itself be watched, while its activity is thus roused, it will be seen (as we have already said, § 167) that its arteries are dilated, and its capillaries filled, and that the blood flows rapidly through the veins in a full stream and of bright arterial hue, frequently with pulsating movements. If a vein of the gland be opened, this large increase of flow, and the lessening of the ordinary deoxygenation of the blood consequent upon the rapid stream, will be still more evident. It is clear that excitation of the chorda largely dilates the arteries; the nerve acts energetically as a vaso-dilator nerve.

Thus stimulation of the chorda brings about two events: a dilation of the blood vessels of the gland, and a flow of saliva. The question at once arises, Is the latter simply the result of the former or is the flow caused by some direct action on the secreting cells, apart from the increased blood-supply? In support of the former view we might argue that the activity of the epithelial secreting cell, like that of any other form of protoplasm, is dependent on blood-supply. When the small arteries of the gland dilate, while the pressure in the arteries on the side towards the heart is (as we have previously seen when treating generally of blood-pressure § 120) correspondingly diminished, the pressure on the far side in the capillaries and veins is increased; hence the capillaries become fuller, and more blood passes through them in a given time. From this we might infer that a larger amount of nutritive material would pass away from the capillaries into the surrounding lymph-spaces, and so into the epithelium cells, the result of which would naturally be to quicken the processes going on in the cells, and to stir these up to greater activity. But even admitting all this it does not necessarily follow that the activity thus excited should take on the form of secretion. It is quite possible to conceive that the increased blood-supply should lead only to the accumulation in the cell of the constituents of the saliva, or of the raw materials for their construction, and not to a discharge of the secretion. A man works better for being fed, but feeding does not make him work in the absence of any stimulus. The increased blood-supply therefore, while favourable to active secretion, need not necessarily bring it about. Moreover, the following facts distinctly shew that it need not. When a cannula is tied into the duct and the chorda is energetically stimulated, the pressure acquired by the saliva accumulated in the cannula and in the duct may exceed for the time being the arterial blood-pressure, even that of the carotid artery; that is to say, the pressure of fluid in the gland outside the blood vessels is greater than that of the blood inside the blood vessels. This must, whatever be the exact mode of transit of nutritive material through the vascular walls, tend to check that transit. Again, if the head of an animal be rapidly cut off, and the chorda immediately stimulated, a flow of saliva takes place far too copious to be accounted for by the emptying of the salivary channels through any supposed contraction of their walls. In this case secretion is excited in the gland though the blood-supply is limited to the small quantity still remaining in the blood vessels. Lastly, if a small quantity of atropin be injected into the veins, stimulation of the chorda produces no secretion of saliva at all, though the dilation of the blood vessels takes place as usual; in spite of the greatly increased blood-supply no secretion at all takes place. These facts prove that the secretory activity is not simply the result of vascular changes, but may be called forth independently; they further lead us to suppose that the chorda contains two sets of fibres, one which we may call secretory fibres, acting directly on the secreting structures only, and the other vaso-dilator fibres, acting on the blood vessels only, and further that atropin, while it has no effect on the latter, paralyses the former just as it paralyses the inhibitory fibres of the vagus. Hence when the chorda is stimulated, there pass down the nerve, in addition to impulses affecting the blood-supply, impulses affecting directly the protoplasm of the secreting cells, and calling it into action, just as similar impulses call into action the contractility of the substance of a muscular fibre. Indeed the two things, secreting activity and contracting activity, are very parallel. We know that when a muscle contracts, its blood vessels dilate; and much in the same way as by atropin the secreting action of the gland may be isolated from the vascular dilation, so (in the frog at all events) by a proper dose of urari muscular contraction may be removed, and leave dilation of the blood vessels as the only effect of stimulating the muscular nerve. In both cases the greater flow of blood may be an adjuvant to, but is not the exciting cause of, the activity of the structures.

Since the chorda acts thus directly on the secreting cells, we should expect to find an anatomical connection between the cells and the nerve; and some authors have maintained that the nerve-fibres may be traced into the cells. But, save perhaps in the case of certain glands of invertebrates (so-called salivary glands of *Blatta*), the evidence as we have said is as yet not convincing.

§ **228**. When the cervical sympathetic is stimulated, the vascular effects, as we have already said, § 168, are the exact contrary of those seen when the chorda is stimulated. The small arteries are constricted, and a small quantity of dark venous blood escapes by the veins. Sometimes, indeed, the flow through the gland is almost arrested. The sympathetic therefore acts as a vaso-constrictor nerve, and in this sense is antagonistic to the chorda.

As concerns the flow of saliva brought about by stimulation of the sympathetic, in the case of the submaxillary gland of the dog the effects are very peculiar. A slight flow results, and the saliva so secreted is remarkably viscid, of higher specific gravity, and richer in corpuscles and in the above-mentioned amorphous lumps, than is the chorda saliva. This action of the sympathetic is little or not at all affected by atropin.

In the submaxillary gland of the dog then the contrast between the effects of chorda stimulation and those of sympathetic stimulation are very marked: the former gives rise to vascular dilation with a copious flow of fairly limpid saliva poor in solids, the latter to vascular constriction with a scanty flow of viscid saliva richer in solids. And in other animals a similar contrast prevails, though with minor differences. Thus in the rabbit both chorda saliva and sympathetic saliva are limpid and free from mucus, though the latter contains more proteids; in the cat, chorda saliva is more viscid than sympathetic saliva; but in both these cases, as in the dog, stimulation of the chorda causes a copious flow with dilated blood vessels, and stimulation of the sympathetic a scanty flow with vascular constriction. We shall return again presently to these different actions of the two nerves; meanwhile we have seen enough of the history of the submaxillary gland to learn that secretion in this instance is a reflex action, the efferent impulses of which directly affect the secreting cells, and that the vascular phenomena may assist, but are not the direct cause of, the flow.

§ **229**. We have dwelt long on this gland because it has been more fruitfully studied than any other. But the nervous mechanisms of the other salivary glands are in their main features similar. Thus the secretion of the parotid gland, like that of the submaxillary, is governed by two sets of fibres: one of cerebro-spinal origin, running along the auriculo-temporal branch of the fifth nerve but originating possibly in the glossopharyngeal, and the other of sympathetic origin coming from the cervical sympathetic. Stimulation of the cerebro-spinal fibres produces a copious flow of limpid saliva, free from mucus, the secretion reaching in the dog a pressure of 118 mm. mercury; stimulation of the cervical sympathetic gives rise in the rabbit to a secretion also free from mucus but rich in proteids and of greater amylolytic power than the cerebro-spinal secretion; in the dog little or no secretion is produced, though, as we shall see later on, certain changes are brought about in the gland itself. In both animals the cerebro-spinal fibres are vaso-dilator, and the sympathetic fibres vaso-constrictor in action. Stimulation of the central end of the glossopharyngeal produces by reflex action a secretion from the parotid gland, but that of the lingual is said to be without effect.

§ **230**. *The secretion of gastric juice.* Though a certain amount of gastric juice may sometimes be found in the stomachs of fasting animals, it may be stated generally that the stomach, like the salivary glands, remains inactive, yielding no secretion, so long as it is not stimulated by food or otherwise. The advent of food into the stomach however at once causes a copious flow of gastric juice; and the quantity secreted in the twenty-four hours is probably very considerable, but we have no trustworthy data for calculating the exact amount. So also when the gastric mucous membrane is stimulated mechanically, as with a feather, secretion is excited: but to a very small amount even when the whole interior surface of the stomach is thus repeatedly stimulated. The most efficient stimulus is the natural stimulus, viz. food; though dilute alkalis seem to have unusually powerful stimulating effects; thus the swallowing of saliva at once provokes a flow of gastric juice. During fasting the gastric membrane is of a pale grey colour, somewhat dry, covered with a thin layer of mucus, and thrown into folds; during digestion it becomes red, flushed, and tumid, the folds disappear, and minute drops of fluid appearing at the mouths of the glands, speedily run together into small streams. When the secretion is very active, the blood flows from the capillaries into the veins in a rapid stream without losing its bright arterial hue. The secretion of gastric juice is in fact accompanied by vascular dilation in the same way as is the secretion of saliva.

§ **231**. Seeing that, unlike the case of the salivary secretion, food is brought into the immediate neighbourhood of the secreting cells, it is exceedingly probable that a great deal of the secretion is the result of the working of a local mechanism; and this view is supported by the fact that when a mechanical stimulus is applied to one spot of the gastric membrane the secretion is limited to the neighbourhood of that spot and is not excited in distant parts. This local mechanism may be nervous in nature or the effect of the stimulus may perhaps be conveyed directly from cell to cell, from the mouth of the gland to its extreme base, without the intervention of any nervous elements; but the vascular changes at least would seem to imply the presence of a nervous mechanism.

The stomach is supplied with nerve-fibres from the two vagi nerves and from the solar plexus of the splanchnic system. The two vagi after forming the œsophageal plexus on the œsophagus are gathered together again as two main trunks which run along the œsophagus, the left in the front the right at the back, to the stomach. The left, or anterior nerve is distributed to the smaller curvature and the front surface of the stomach, forming a plexus in which nerve-cells are present; and branches pass on to the liver and probably to the duodenum. The right, or posterior nerve is distributed to the hinder surface of the stomach, but only to the extent of about one-third of its fibres; about two-thirds of the fibres pass on to the solar plexus. The fibres of the vagus nerves thus distributed to the stomach are for the most part non-medullated fibres; by the time the vagus reaches the abdomen it consists almost exclusively of non-medullated fibres, medullated fibres being very few; the large number of medullated fibres which the nerve contains in the upper part of the neck pass off into the laryngeal, cardiac and other branches.

From the solar plexus nerves, arranged largely in plexuses, pass in company with the divisions of the coeliac artery, coronary artery of the stomach and branches of the hepatic artery, to the stomach. Though the two abdominal splanchnic nerves which join the solar plexus (semilunar ganglia) are chiefly composed of medullated fibres, the nerves which pass from the plexus to the stomach are to a large extent composed of non-medullated fibres. All these nerves, both the branches of the vagi and those from the solar plexus, lie at first in company with the arteries on the surface of the stomach beneath the peritoneum. From thence they pass inwards, still in company with arteries, and form on the one hand a plexus, containing nerve-cells, between the longitudinal and circular muscular coats corresponding to what in the intestine we shall have to speak of as the plexus of Auerbach, whence fibres are distributed to the two muscular coats, and on the other hand a plexus in the submucous coat, also containing nerve-cells, corresponding to what is known in the intestine as Meissner's plexus. From this latter plexus fibres pass to the mucous membrane; some of these end in the muscularis mucosæ; whether any are connected with the gastric glands, and if so how, is not at present known.

There are no facts which afford satisfactory evidence that any part of this arrangement of nerves supplies such a local nervous mechanism as was suggested above. The importance however of such a local mechanism whatever its nature, and the subordinate value of any connection between the gastric membrane and the central nervous system, is further shewn by the fact that a secretion of quite normal gastric juice will go on after both vagi, or the nerves from the solar plexus going to the stomach have been divided, and indeed when all the nervous connections of the stomach are as far as possible severed. And all attempts to provoke or modify gastric secretion by the stimulation of the nerves going to the stomach, have hitherto failed. On the other hand, in cases of gastric fistula, where by complete occlusion of the œsophagus stimulation by the descent of saliva has been avoided, the mere sight or smell of food has been seen to provoke a lively secretion of gastric juice. This must have been due to some nervous action; and the same may be said of the cases where emotions of grief or anger suddenly arrest the secretion going on or prevent the secretion which would otherwise have taken place as the result of the presence of food in the stomach. So that much has yet to be learnt in this matter.

§ **232**. The contrast presented between the scanty secretion resulting from mechanical stimulation and the copious flow which actual food induces is interesting because it seems to shew that the secretory activity of the cells is heightened by the absorption of certain products derived from the portions of food first digested. This is well illustrated by the following experiment of Heidenhain. This observer, adopting the method employed for the intestine, of which we shall speak later on, succeeded in isolating a portion of the fundus from the rest of the stomach; that is to say, he cut out a portion of the fundus, sewed together the cut edges of the main stomach, so as to form a smaller but otherwise complete organ, while by sutures he converted the excised piece of fundus into a small independent stomach opening on to the exterior by a fistulous orifice. When food was introduced into the main stomach secretion also took place in the isolated fundus. This at first sight might seem the result of a nervous reflex act; but it was observed that the secondary secretion in the fundus was dependent on actual digestion taking place in the main stomach. If the material introduced into the main stomach were indigestible or digested with difficulty, so that little or no products of digestion were formed and absorbed into the blood, such *ex. gr.* as pieces of ligamentum nuchæ, very little secretion took place in the isolated fundus. We quote this now as bearing on the question of a possible nervous mechanism of gastric secretion, but we shall have to return to it under another aspect.

The changes in a gland constituting the act of secretion.

§ **233**. We have now to consider what are the changes in the glandular cells and their surroundings which cause this flow of fluid possessing specific characters into the lumen of an alveolus, and so into a duct. It will be convenient to begin with the pancreas.

The thin extended pancreas of a rabbit may, by means of special precautions, be spread out on the stage of a microscope and examined with even high powers, while the animal is not only alive but under such conditions that the gland remains in a nearly normal state, capable of secreting vigorously. It is possible under these circumstances to observe even minutely the appearances presented by the gland when at rest and loaded, and to watch the changes which take place during secretion.

When the animal has not been digesting for some little time, and the gland is therefore "loaded," the outlines of the individual cells, as we have already said, § 220, are very indistinct, the lumen of the alveolus is invisible or very inconspicuous, and each cell is crowded with small, refractive spherical granules, forming an irregular granular mass which hides the nucleus and leaves only a very narrow clear outer zone next to the basement membrane, or it may be hardly any such zone at all. Fig. 63 *A*.

The blood-supply moreover is scanty, the small arteries being constricted and the capillaries imperfectly filled with corpuscles.

If, however, the same pancreas be examined while it is in a state of activity, either from the presence of food in the stomach, or from the injection of some stimulating drug, such as pilocarpin, a very different state of things is seen. The individual cells (Fig. 63 *B*) have become smaller and much more distinct in outline, and the contour of the alveolus which previously was even is now wavy, the basement membrane being indented at the junctions of the cells; also the lumen of the alveolus is now wider and more conspicuous. In each cell the granules have become much fewer in number and as it were have retreated to the inner margin, so that the inner granular zone is much narrower and the outer transparent zone much broader than before; the latter too is frequently marked at its inner part by delicate striæ running into the inner zone. At the same time the blood vessels are

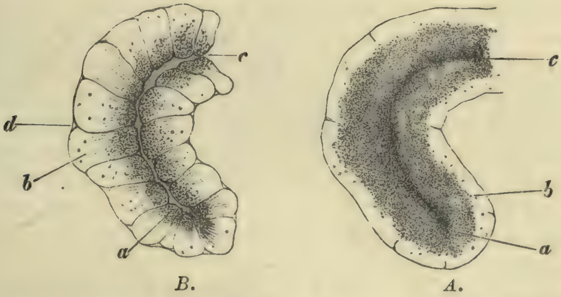

FIG. 63. A PORTION OF THE PANCREAS OF THE RABBIT. (Kühne and Sheridan Lea.) *A* at rest, *B* in a state of activity.

a the inner granular zone, which in *A* is larger, and more closely studded with fine granules, than in *B*, in which the granules are fewer and coarser.

b the outer transparent zone, small in *A*, larger in *B*, and in the latter marked with faint striæ.

c the lumen, very obvious in *B*, but indistinct in *A*.

d an indentation at the junction of two cells, seen in *B*, but not occurring in *A*.

largely dilated and the stream of blood through the capillaries is full and rapid.

With care the change from the one state of things to the other may be watched under the microscope. The vascular changes can of course be easily appreciated, but the granules may also be seen to diminish in number. Those at the inner margin seem to be discharged into the lumen, and those nearer the outer margin to travel inwards through the cell-substance towards the lumen, the faint striæ spoken of above, apparently at all events, being the marks of their paths. Obviously during secretion, the granules with which the cell-substance was 'loaded' are 'discharged' from the cell into the lumen of the alveolus. What changes these granules may undergo during the discharge we shall consider presently.

Sections of the prepared and hardened pancreas of any animal tell nearly the same tale as that thus told by the living pancreas of the rabbit. In sections for instance of the pancreas of a dog which has not been fed, and therefore has not been digesting, for some hours (24 or 30), the cells are seen to be crowded with granules (which however are usually shrunken and irregular owing to the influence of the hardening agent), leaving a very narrow outer zone. In similar sections of the pancreas of a dog which has been recently fed, six hours before for example, and in which therefore the gland has been for some time actively secreting, the granules are far less numerous, and the clear outer zone accordingly much broader and more conspicuous. With osmic acid these granules stain well, and are preserved in their spherical form, so that the cell thus stained maintains much of the appearance of a living cell. But with carmine, hæmatoxylin &c. the granules do not stain nearly so readily as does the cell-substance of the cells, so that a discharged cell stains more deeply than does a loaded cell because the staining of the 'protoplasmic' cell-substance is not so much obscured by the unstained granules; besides which however the actual cell-substance stains probably somewhat more deeply in the discharged cell. It may be added that in the discharged cell the nucleus is conspicuous and well formed; in the loaded cell it is generally in prepared sections, more or less irregular, possibly because in these it is less dense and more watery than in the discharged cell, and so shrinks under the influence of the reagents employed.

These several observations suggest the conclusion that in a gland at rest the cell is occupied in forming by means of the metabolism of its cell-substance and lodging in itself (§ 30) certain granules of peculiar substance intended to be a part and probably an important part of the secretion. This goes on until the cell is more or less completely 'loaded.' In such a cell the amount of actual living cell-substance is relatively small, its place is largely occupied by granules, and it itself has been partly consumed in forming the granules. During the act of secretion the granules are discharged to form part of the secretion, other matters including water, as we shall see, making up the whole secretion; and the cell would be proportionately reduced in size were it not that the act of the discharge seems to stimulate the cell-substance to a new activity of growth, so that new cell-substance is formed; this however is in turn soon in part consumed in order to form new granules. And what is thus seen with considerable distinctness and ease in the pancreas, is seen with more or less distinctness in other glands.

§ **234**. When we study an albuminous gland, the parotid gland for instance, in a living state, we find that the changes which take place during activity are quite comparable to those of the pancreas. During rest (Fig. 64 *A*), the cells are large, their outlines very indistinct, in fact almost invisible, and the cell-substance is studded with granules. During activity (Fig. 64 *B*), the cells become smaller, their outlines more distinct, and the granules disappear, especially from the outer portions of each cell. After prolonged activity, as in Fig. 64 *C*, the cells are still smaller with their outlines still more distinct, and the granules have disappeared almost entirely, a few only being left at the extreme inner margin of each cell, abutting upon the conspicuous, almost gaping lumen of the alveolus. And upon special examination it is found that the nuclei are large and round. In fact we might almost take the parotid, as thus studied, to be more truly typical of secretory changes than even the pancreas. For, the demarcation of an inner and outer zone is not a necessary feature of a secreting cell at rest. What is essential is that the cell-substance manufactures material, which for a while, that is during rest, is deposited in the cell, generally in the form of granules but not necessarily so, and that during activity this material is used up, the disappearance

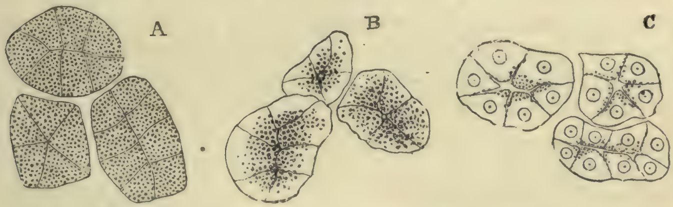

FIG. 64. CHANGES IN THE PAROTID DURING SECRETION. (Langley.)

The figure, which is somewhat diagrammatic, represents the microscopic changes which may be observed in the *living* gland. *A*. During rest. The obscure outlines of the cells are introduced to shew the relative size of the cells, they could not be readily seen in the specimen itself. *B*. After moderate stimulation. *C*. After prolonged stimulation. The nuclei are diagrammatic, and introduced to shew their appearance and position.

of the granules, when these are visible, being naturally earliest and most marked at the outer portions of each cell, and progressing inwards towards the lumen, the whole cell becoming smaller and as it were shrunken.

In the cells of the parotid gland and other albuminous cells the granules seen in the living or fresh cell differ from the granules seen in the pancreatic cell, inasmuch as they are easily dissolved or broken up by the action of alcohol, chromic acid, and the other usual hardening reagents, and hence in hardened specimens have disappeared. In consequence, in sections of hardened and prepared albuminous glands the difference between resting or loaded and active or discharged cells may appear not very conspicuous; and this is especially the case in the parotid gland of the rabbit when the activity has been called into play by stimulation of the auriculo-temporal nerve. When however, either in the rabbit or the dog, the cervical sympathetic is stimulated, though the stimulation gives rise in the rabbit to little secretion of saliva, and in the dog to none at all, a marked effect on the gland is produced, and changes, in the same direction as those already described, may be observed. During rest, the cells of the parotid as seen in sections of the gland hardened in alcohol (Fig. 65 *A*) are pale, transparent, staining with difficulty, and the nuclei possess irregular outlines as if shrunken by the reagents employed. After stimulation of the sympathetic, the protoplasm of the cells becomes turbid (Fig. 65 *B*), and stains much more readily, while the nuclei are no longer irregular in outline but round and large, with conspicuous nucleoli, the whole cell at the same time, at least after prolonged stimulation, becoming distinctly smaller.

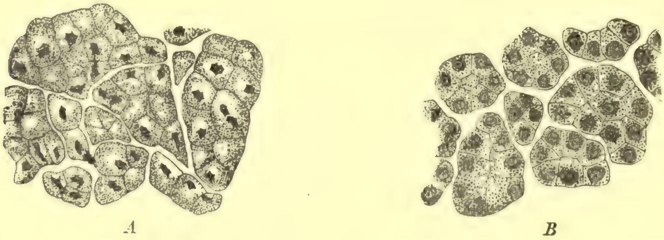

FIG. 65. SECTIONS OF THE PAROTID OF THE RABBIT. *A* at rest, *B* after stimulation of the cervical sympathetic. Both sections are from *hardened* gland. (After Heidenhain.)

§ **235**. In a mucous gland the changes which take place are of a like kind, though apparently somewhat more complicated, owing probably to the peculiar characters of the mucin which is so conspicuous a constituent of the secretion.

If a piece of resting, loaded submaxillary gland be teased out, while fresh and warm from the body, in normal saline solution, the cell-substance of the mucous cells (Fig. 66 *a*) is seen to be crowded with granules or spherules which may fairly be compared with the granules of the pancreas, though perhaps less dense and solid than these.

If a piece of a gland which has been secreting for some time, and is therefore a discharged gland, be examined in the same way (Fig. 66 *b*) the granules are far less numerous and largely confined to the part of the cell nearer the lumen, the outer part of the cell around the nucleus consisting of ordinary 'protoplasmic' cell-substance. The distinction however between an inner 'granular zone' next to the lumen and an outer 'clear zone' next to the basement membrane is less distinct than in the pancreas, partly because the granules do not disappear in so regular a manner as in the pancreas and partly because the outer zone of the mucous cell, as it forms, is less homogeneous than that of the pancreatic cell.

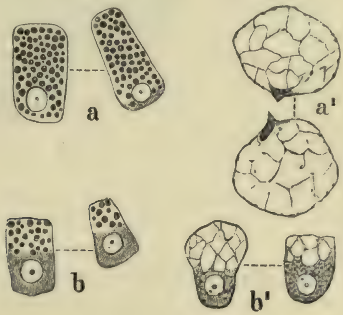

FIG. 66. MUCOUS CELLS FROM A FRESH SUBMAXILLARY GLAND OF DOG. (Langley.)

a and *b* isolated in 2 p.c. salt solution: *a*, from loaded gland, *b* from discharged gland (the nuclei are usually more obscured by granules than is here represented).

(On teasing out a fragment of fresh in 2 to 5 p.c. salt solution, the cells usually become broken up so that isolated cells are rarely obtained entire; isolated cells are common if the gland be left in the body for a day after death.)

a′, *b′*, treated with dilute acid: *a′* from loaded, *b′* from discharged gland.

The 'granules' or 'spherules' of the mucous cell are moreover of a peculiar nature. If the fresh cell, shewing granules, (either many as in the case of a loaded or few as in the case of a discharged cell) be irrigated with water or with dilute acids or dilute alkalis the granules swell up (Fig. 66 *a′*, *b′*) into a transparent mass, giving the reactions of mucin, traversed by a network of 'protoplasmic' cell-substance. In this way is produced an appearance very similar to that shewn in sections of mucous glands hardened and stained in the ordinary way.

As we have already said (§ 216) in the loaded mucous cell in such hardened and stained preparations (Fig. 67 *a*) there is seen a small quantity of protoplasmic cell-substance gathered round the nucleus at the outer part of the cell next to the basement membrane; the rest of the cell consists of a network of cell-substance, the interstices being filled with transparent material, which, unlike the network itself and the mass of cell-substance round the nucleus, does not stain with carmine or with certain other dyes. The discharged cell in similar preparations (Fig. 67 *b*) differs from the loaded cell in the amount of transparent non-staining material being much less and chiefly confined to the inner part of the cell, while the protoplasmic cell-substance around the now large and well-formed nucleus is not only, both relatively and absolutely, greater in amount, but stains still more deeply than in the loaded cell.

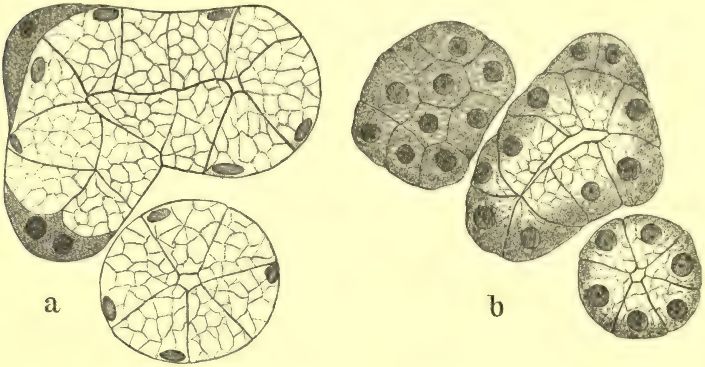

Fig. 67. Alveoli of Dog's Submaxillary Gland hardened in alcohol and stained with carmine. (Langley.) (The network is diagrammatic.)

a, from a loaded gland.

b, from a discharged gland; the chorda tympani having been stimulated at short intervals during five hours.

It would appear therefore that in the mucous cell, as in the pancreatic cell, the cell-substance forms and deposits in itself certain material in the form of granules. During secretion these granules disappear and presumably form part of the secretion. But the granules of a mucous cell differ from those of the pancreatic cell in as much as they are apt under the influence of reagents to be transformed, while still within the cell, into the transparent viscid material which we call mucin; hence the appearances presented by sections of hardened glands. It seems natural to infer that the granules consist not of mucin itself but of a forerunner of mucin, of some substance which can give rise to mucin, and which we might call mucigen. And we might further infer that during the act of secretion the granules of mucigen are transformed into masses of mucin and so discharged from the cell. Under this view the appearances presented by the hardened glands, as distinguished from the living glands, might be interpreted as indicating that under the influence of the reagents employed, the mucigen of the loaded cells had undergone the transformation into mucin without being discharged from the cells. Up to the present however it has not been found possible to isolate from the gland any definite body, capable of being converted into mucin, and there are some reasons for thinking that not only the granules but part also of the substance between them contributes to the formation of mucin. Apart from this complication, however, the general course of events in the mucous cell seems to be the same as in the pancreatic cell; the cell-substance manufactures and loads itself with a special product, (or special products); during the act of secretion, this product, undergoing at the time a certain amount of change, is discharged from the cell to form part of the secretion, and the cell-substance, stirred up to increased growth, subsequently manufactures a new supply of the product.

§ **236**. The 'central' or 'chief' cells of the gastric glands also exhibit similar changes. In such an animal as the newt these cells may, though with difficulty, be examined in the living state. They are then found to be studded with granules when the stomach is at rest. During digestion these granules become much less numerous and are chiefly gathered near the lumen, leaving in each cell a clear outer zone. And in many mammals the same abundance of granules in the loaded cell, the same paucity of granules for the most part restricted to an inner zone in the discharged cell, may be demonstrated by the use of osmic acid, Fig. 68.

When the stomach is hardened by alcohol these changes, like the similar changes in an albuminous cell, are obscured by the shrinking of the 'granules' or by their swelling up and becoming diffused through the rest of the cell-substance; so that though, in sections so prepared, very striking differences are seen between loaded and discharged cells, these are unlike those seen in living glands. In specimens taken from an animal which has not been fed for some time, the central cells of the gastric glands are pale, finely granular, and do not stain readily with carmine and other dyes. During the early stages of gastric digestion, the same cells are found somewhat swollen, but turbid and more coarsely granular; they stain much more readily. At a later stage they become smaller and shrunken, but are even more turbid and granular than before, and stain still more deeply. This is true, not only of the central cells in the cardiac glands, but also of the cells of which the pyloric glands are built up. In the loaded cell very little staining takes place, because the amount of living staining cell-substance is small relatively to the amount of material with which it is loaded and which does not

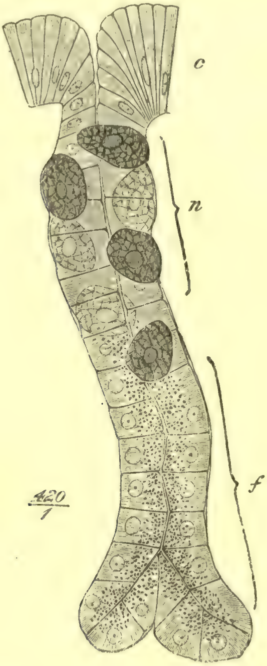

Fig. 68. Gastric Gland of Mammal (Bat) during activity. (Langley.)

c, the mouth of the gland with its cylindrical cells.

n, the neck, containing conspicuous ovoid cells, with their coarse protoplasmic network.

f, the body of the gland. The granules are seen in the central cells to be limited to the inner portions of each cell, the round nucleus of which is conspicuous.

stain readily. In the cell which after great activity has discharged itself, the cell is smaller, but what remains is largely living cell-substance, some of it new, and all staining readily. It would appear also that during the activity of the cell some substances, capable of being precipitated by alcohol, make their appearance, and the presence of this material adds to the turbid and granular aspect of the cell; possibly also this material contributes to the staining. A similar material seems to make its appearance in the cells of albuminous glands.

In the ovoid or border cells no very characteristic changes make their appearance. During digestion they become larger, more swollen as it were, and in consequence bulge out the basement membrane, but no characteristic disappearance of granules can be observed. In the living state, the cell-substance of these ovoid cells appears finely granular, but in hardened and prepared sections has a coarsely granular, "reticulate" look which is perhaps less marked in the swollen active cells than in the resting cells.

§ **237**. All these various secreting cells then, pancreatic cell, mucous cell, albuminous cell, and central gastric cell, exhibit the same series of events, modified to a certain extent in the several cases. In each case the 'protoplasmic' cell-substance manufactures and lodges in itself material destined to form part of the juice secreted. In the fresh cell this material may generally be recognized under the microscope by its optical characters as granules; these however are apt to become altered by reagents. But we must guard ourselves against the assumption that the material which can thus be recognized is the only material thus stored up; we may, in future, by chemical or other means be able to differentiate other parts of the cell-body as being also material similarly stored up.

During activity, while the gland is secreting, this material, either unchanged or after undergoing change, is wholly or partially discharged from the cell. The cell in consequence of having thus got rid of more or less of its load consists to a larger extent of actual living cell-substance, this being in many cases increased by rapid new growth, though the bulk of the discharged cell may be less than that of the loaded cell.

This activity of growth continues after the act of secretion, but the discharged cell soon begins again the task of loading itself with new secretion material for the next act of secretion.

Thus in most cases there is, corresponding to the intermittence of secretion, an alternation of discharge and loading; but it must be borne in mind that such an alternation is not absolutely necessary even in the case of intermittent secretion. We can easily imagine that the discharge, say, of 'granules' during secretion should stir up the cell to an increased activity in forming granules, and that the formative activity should cease when the secretory activity ceased. In such a case the number of new granules formed might always be equal to the number of old granules used up, and the active cell in spite of its discharge would possess as many granules, that is to say, as large a load, as the cell at rest. And in the central gastric cells of some animals it would appear that such a continued balancing of load and discharge does actually take place, so that no distinction in granules can be observed between resting and active cells.

§ **238**. We spoke just now of the material stored up in the cell and destined to form part of the secretion as undergoing change before it was discharged. In the mucous cell we have seen that the material deposited in the living cell has at first the form of granules. These granules however are easily converted into a transparent material lodged in the spaces of the cell-substance, which material even if not exactly identical with at least closely resembles the mucin found in the secretion; and apparently, in the act of secretion the granules do undergo some such change. In the case of some other glands moreover we have chemical as well as optical evidence that the material stored up in the cell, is, in part at least, not the actual substance appearing in the secretion but an antecedent of that substance.

An important constituent of pancreatic juice is, as we shall see later on, a body called *trypsin*, a ferment very similar to pepsin, acting on proteid bodies and converting them into peptone and other substances. Though in many respects alike, pepsin and trypsin are quite distinct bodies, and differ markedly in this, that while an acid medium is necessary for the action of pepsin, an alkaline medium is necessary for the action of trypsin; and accordingly the pancreatic juice is alkaline in contrast to the acidity of gastric juice. Trypsin, can, like pepsin (§ 205), be extracted with glycerine from substances in which it occurs; glycerine extracts of trypsin however need for the manifestation of their powers the presence of a weak alkali, such as a 1 p.c. solution of sodium carbonate.

Now trypsin is present in abundance in normal pancreatic juice; but a loaded pancreas, one which is ripe for secretion, and which if excited to secrete would immediately pour out a juice rich in trypsin, contains no trypsin or a mere trace of it; nay even a pancreas which is engaged in the act of secreting contains in its actual cells an insignificant quantity only of trypsin, as is shewn by the following experiment.

If the pancreas of an animal, even of one in full digestion, be treated, *while still warm from the body*, with glycerine, the glycerine extract, as judged of by its action on fibrin in the presence of sodium carbonate, is inert or nearly so as regards proteid bodies. If, however, the same pancreas be kept for 24 hours before being treated with glycerine, the glycerine extract readily digests fibrin and other proteids in the presence of an alkali. If the pancreas, while still warm, be rubbed up in a mortar for a few minutes with dilute acetic acid, and then treated with glycerine, the glycerine extract is strongly proteolytic. If the glycerine extract obtained without acid from the warm pancreas, and therefore inert, be diluted largely with water, and kept at 35° C. for some time, it becomes active. If treated with acidulated instead of distilled water, its activity is much sooner developed. If the inert glycerine extract of warm pancreas be precipitated with alcohol in excess, the precipitate, inert as a proteolytic ferment when fresh, becomes active when exposed for some time in an aqueous solution, rapidly so when treated with acidulated water. These facts shew that a pancreas taken fresh from the body, even during full digestion, *contains but little ready-made ferment*, though there is present in it a body which, by some kind of decomposition, *gives birth to the ferment.* We may remark incidentally that though the presence of an alkali is essential to the proteolytic action of the actual ferment, the formation of the ferment out of its forerunner is favoured by the presence of a small quantity of acid; the acid must be used with care, since the trypsin, once formed, is destroyed by acids. To this body, this mother of the ferment, which has not at present been satisfactorily isolated, but which appears to be a complex body, splitting up into the ferment, which as we have seen is at all events not certainly a proteid body, and into an undeniably proteid body, the name of *zymogen* has been applied. But it is better to reserve the term zymogen as a generic name for all such bodies as not being themselves actual ferments, may by internal changes give rise to ferments, for all 'mothers of ferment' in fact; and to give to the particular mother of the pancreatic proteolytic ferment, the name *trypsinogen.*

Evidence of a similar kind shews that the gastric glands, both the cardiac and the pyloric glands, while they contain comparatively little actual pepsin, contain a considerable quantity of a zymogen of pepsin, or *pepsinogen*; and there can be little doubt but that this pepsinogen is lodged in the central cells of the cardiac glands and in the somewhat similar cells which line the whole of the pyloric glands.

It is further interesting to observe that, as a general rule, the amount of trypsinogen in a pancreas at any given time rises and sinks *pari passu* with the granular inner zone, *i.e.* with the amount of granules in the cell. The wider the inner zone and the more abundant the granules the larger the amount, the narrower the zone and the fewer the granules the smaller the amount, of trypsinogen; and in the cases of old-established fistulæ, where the secretion is wholly inert on proteids, the inner granular zone is absent from the cells. And the same parallelism has been observed between the abundance of granules in the central cells and the quantity of pepsinogen present in the gastric glands.

The parallelism however, at all events in the case of the pancreas, appears not to be absolute, for it is stated that in the pancreas of dogs after long starvation there is little or no trypsinogen in the gland and yet the cells exhibit a marked inner zone of granules. Moreover we should not, in any case, be justified in concluding that the granules of the pancreatic cell are wholly composed of trypsinogen; for, as we shall presently see, the pancreatic juice contains besides trypsin not only other important ferments but also certain proteid constituents; and the granules, which are of a proteid nature, probably supply these proteids of the juice. Hence the parallelism between granules and trypsinogen is at best an incomplete one. But even such an incomplete parallelism is of value. The granules whatever their nature are products of the metabolism of the cell, lodged for a while in the cell-substance but eventually discharged; and certain of the constituents of the several secretions, such as mucin, trypsin, pepsin and the like appear to be in a similar way products of the metabolism of the cell, lodged for a while in the cell-substance, not in all cases exactly in the condition in which they will be discharged from the cell, but in an antecedent phase such as zymogen or the like, and in all cases ultimately ejected from the cell, to supply part and generally the important part of the secretion.

§ **239**. *The act of secretion itself.* The above discussion prepares us at once for the statement that the old view of secretion according to which the gland picks out, separates, secretes (hence the name secretion) and so filters as it were from the common store of the blood the several constituents of the juice, is untenable. According to that view the specific activity of any one gland was confined to the task of letting certain constituents of the blood pass from the capillaries surrounding the alveolus through the cells to the channels of the ducts, while refusing a passage to others. We now know that certain important constituents of each juice, the pepsin of gastric juice, the mucin of saliva and the like are formed in the cell, and not obtained ready made from the blood. A minute quantity of pepsin does exist it is true in the blood, but there are reasons for thinking that this has made its way back into the blood, either being absorbed from the interior of the stomach or, as seems more probable, picked up directly from the gastric glands; and so with some of the other constituents of other juices. The chief or specific constituents of each juice are formed in the cell itself.

But the juice secreted by any gland consists not only of the specific substances such as mucin, pepsin or other ferment, or other bodies, found in it alone, but also of a large quantity of water, and of various other substances, chiefly salines, common to it, to other juices and to the blood. And the question arises, Is the water, are the salts and other common substances furnished by the same act as that which supplies the specific constituents?

Certain facts suggest that they are not. For instance, as mentioned some time ago, in the submaxillary gland of the dog, stimulation of the chorda tympani produces a copious flow of saliva, which is usually thin and limpid, while stimulation of the cervical sympathetic produces a scanty flow of thick viscid saliva. That is to say, stimulation of the chorda has a marked effect in promoting the discharge of water, while stimulation of the sympathetic has a marked effect in promoting the discharge of mucin. To this we may add the case of the parotid of the dog. In this gland stimulation of a cerebro-spinal nerve, the auriculo-temporal, produces a copious flow of limpid saliva, while stimulation of the sympathetic produces itself little or no secretion at all; but when the sympathetic and cerebro-spinal nerves are stimulated at the same time, the saliva which flows is much richer in solid and especially in organic matter than when the cerebro-spinal nerve is stimulated alone. And we have already seen that in this gland the microscopic changes following upon sympathetic stimulation are more conspicuous than those which follow upon cerebro-spinal stimulation.

These and other facts have led to the conception that the act of secretion consists of two parts, which in one case may coincide, in another may take place apart or in different proportions. On the one hand, there is the discharge of water carrying with it common soluble substances, chiefly salines, derived from the blood; on the other hand, a metabolic activity of the cell-substance gives rise to the specific constituents of the juice. To put the matter broadly, the latter process produces the specific constituents, the former washes these and other matters into the duct. It has been further supposed that two kinds of nerve fibres exist: one governing the former process and, in the case of the submaxillary gland for instance, preponderating, though not to the total exclusion of the other kind, in the chorda tympani; the other governing the latter process and preponderating in the branches of the cervical sympathetic. These have been called respectively 'secretory' and 'trophic' fibres; but these terms are not desirable. It may be here remarked that even the former process is a distinct activity of the gland, and not a mere filtration. For, as we have seen in the case of the salivary glands, when atropin is given, not only do the specific constituents cease to be ejected as a consequence of stimulation of the chorda, but the discharge of water, in spite of the blood vessels becoming dilated, is also arrested: no saliva at all leaves the gland. And what is true of the salivary glands as regards the dependence of the flow of water on something else besides the mere pressure of the blood in the blood vessels, appears to hold good with other glands also. Indeed it has been suggested that the very discharge of water is due to an activity of the cell; the hypothesis has been put forward that changes in the cell give rise to the formation in the cell of substances which absorb water from the blood or lymph on the one side and give it up on the other side into the lumen of the alveolus. Such an hypothesis cannot be regarded as proved; but the mere putting it forward raises doubts as to the validity of the distinction on which we have been dwelling; and other considerations point in the same direction. For instance, if the common soluble salts present in a juice, as distinguished from the specific constituents, were merely carried into the juice by the rush so to speak of water, we should expect to find the percentage of these salts either remaining the same or perhaps decreasing when the juice was secreted more rapidly and in fuller volume. But under these circumstances the percentage very frequently increases; and in general we find that under various circumstances the proportion of salts secreted to the quantity of water secreted may vary considerably. Obviously, while something determines the quantity of water passing into the alveolus, something else determines how much of common soluble salts that water contains, and still something else determines to what extent that water is also laden with specific constituents and other organic bodies. The whole action is too complicated to be described as consisting merely of the two processes mentioned above, but the time has not yet come for clear and definite statements. Everything however tends to shew that the cell is the prime agent in the whole business, though we cannot at present define the nature of the several changes in the cell, nor can we say how those changes are exactly related to each other, to changes of the blood-pressure in the blood vessels, or, we may add, to changes taking place in the lymph-spaces which lie between the blood and the cell.

We may perhaps add that, since in certain cutaneous secreting glands the alveolus, or what corresponds to the alveolus, is wrapped round with plain muscular fibres, the contraction of which appears to force the secretion outwards, the idea has been suggested that in glands, such as we are now considering, the cell-substance making use of "protoplasmic" contraction instead of actual muscular contraction, may force part of the cell contents into the lumen of the alveolus. Such a mode of secretion would be comparable to the ejection of undigested material, or "excretion," by an amœba. But we have no satisfactory evidence in favour of this view.

§ **240**. Throughout the above we have spoken as if the secretion were furnished exclusively by the cells of the alveoli or secreting portion of the gland, as if the epithelium cells lining the ducts, or conducting portion of the gland, contributed nothing to the act. In the gastric glands the slender cells lining the mouths of the glands (which correspond to ducts) and covering the ridges between, are mucous cells secreting into the stomach generally a small, but under abnormal conditions a large amount, of mucus, which has its uses but is not an essential part of the gastric juice. In the salivary glands we can hardly suppose that the long stretch of characteristic columnar epithelium which reaches from the alveoli to the mouth of the long main duct serves simply to furnish a smooth lining to the conducting passages; but we have as yet no clear indications of what the function of this epithelium can be.

§ **241**. Before we leave the mechanism of secretion there are one or more accessory points which deserve attention.

In treating just now of the gastric glands we spoke as if pepsin were the only important constituent of gastric juice, whereas, as we have previously seen, the acid is equally essential. The formation of the free acid of the gastric juice is very obscure, and many ingenious but unsatisfactory views have been put forward to explain it. It seems natural to suppose that it arises in some way from the decomposition of sodium chloride drawn from the blood;

and this is supported by the fact that when the secretion of gastric juice is actively going on, the amount of chlorides leaving the blood by the kidney is proportionately diminished; but nothing definite can at present be stated as to the mechanism of that decomposition. And even admitting that the sodium chloride of the body at large is the ultimate source of the chlorine element of the acid, it appears more likely that that element should be set free in the stomach by the decomposition of some highly complex and unstable chlorine compound previously generated, than that it should arise by the direct splitting-up of so stable a body as sodium chloride at the very time when the acid is secreted.

In the frog, while pepsin free from acid is secreted by the glands in the lower portion of the œsophagus, an acid juice is afforded by glands in the stomach itself, which have accordingly been called *oxyntic* (ὀξύνειν to sharpen, acidulate) glands; but these oxyntic glands appear also to secrete pepsin. In the mammal the isolated pylorus secretes an alkaline juice; in fact, the appearance of an acid juice is limited to those portions of the stomach in which the glands contain both 'chief' or 'central,' and 'ovoid' or 'border' cells. Now from what has been previously said there can be no doubt that the chief cells do secrete pepsin. On the other hand there is no evidence whatever of the formation of pepsin by the 'border' or 'ovoid' cells, though this was once supposed to be the case and these cells were unfortunately formerly called 'peptic' cells. Hence it has been inferred that the border cells secrete acid; but the argument is at present one of exclusion only, there being no direct proof that these cells actually manufacture the acid.

The rennin appears to be formed by the same cells which manufacture the pepsin, that is, by the chief cells of the fundus generally and to some extent by the cells of the pyloric glands. We may add that we have evidence of the existence of a zymogen of rennin analogous to the zymogen of pepsin or of trypsin.

The mucus which is present as a thin layer over the surface of the fasting stomach, and which especially in herbivorous animals is increased during digestion, comes as we have said from the mucous cells which line the mouths of the several glands and cover the intervening surfaces.

§ **242**. We previously called attention to the fact that in the case of the stomach the absorption of the products of digestion largely increased the activity of the secreting cells. This has led to the idea that one effect of food is to 'charge' the gastric cells with pepsinogen, and that certain articles of food might be considered as especially peptogenous, *i.e.* conducive to the formation of pepsin. Such a view is tempting, but needs as yet to be more fully supported by facts.

§ **243**. Seeing the great solvent power of both gastric and pancreatic juice, the question is naturally suggested, Why does not the stomach digest itself? After death, the stomach is frequently found partially digested, viz. in cases when death has taken place suddenly on a full stomach. In an ordinary death, the membrane ceases to secrete before the circulation is at an end. That there is no special virtue in living things which prevents their being digested is shewn by the fact, that the leg of a living frog or the ear of a living rabbit introduced into the stomach of a dog through a gastric fistula is readily digested. It has been suggested that the blood-current keeps up an alkalinity sufficient to neutralize the acidity of the juice in the region of the glands themselves; but this will not explain why the pancreatic juice, which is active in an alkaline medium, does not digest the proteids of the pancreas itself, or why the digestive cells of the bloodless actinozoon or hydrozoon do not digest themselves. We might add, it does not explain why the amœba, while dissolving the protoplasm of the swallowed diatom, does not dissolve its own protoplasm. We cannot answer this question at all at present, any more than the similar one, why the delicate protoplasm of the amœba resists during life the entrance into itself by osmosis of more water than it requires to carry on its work, while a few moments after it is dead water enters freely by osmosis, and the effects of that entrance become abundantly evident by the formation of bullæ and the breaking up of the protoplasm.

SEC. 4. THE PROPERTIES AND CHARACTERS OF BILE, PANCREATIC JUICE AND SUCCUS ENTERICUS.

§ 244. In the living body the food, subjected to the action first of the saliva and then of the gastric juice, undergoes in the stomach changes which we shall presently consider in detail, and the food so changed is passed on into the small intestine, where it is further subjected to the action of the bile secreted by the liver, of pancreatic juice secreted by the pancreas, and possibly to some extent, though this is by no means certain, of a juice secreted by the intestine itself, and called *succus entericus.* It will be convenient to study the minute structure of the liver in connection with other functions of the liver more important perhaps than that of the secretion of bile, namely the formation of glycogen, and other metabolic events occurring in the hepatic cells; we have already studied the structure of the pancreas; and the structure of the intestine will best be considered by itself. We therefore turn at once to the properties and characters of the above-named juices.

Bile.

Though bile, after secretion in the lobules of the liver, is passed on along the hepatic duct, it is in the case of most animals not poured at once into the duodenum but taken by the cystic duct to the reservoir of the gall-bladder. Here it remains, until such time as it is needed, when a quantity is poured along the common bile duct into the intestine.

The quality of bile varies much, not only in different animals, but in the same animal at different times. It is moreover affected by the length of the sojourn in the gall-bladder; bile taken direct from the hepatic duct, especially when secreted rapidly, contains little or no mucus; that taken from the gall-bladder, as of slaughtered oxen or sheep, is loaded with mucus. The colour of the bile of carnivorous and omnivorous animals, and of man, is generally a bright golden red: of herbivorous animals, a yellowish green, or a bright green, or a dirty green, according to circumstances, being much modified by retention in the gall-bladder. The reaction is neutral or alkaline. The following may be taken as the average composition of human bile taken from the gall-bladder, and therefore containing much more mucus as well as, relatively to the solids, more water than bile from the hepatic duct.

		In 1000 parts.
Water		859·2
Solids:—		
Bile Salts	91·4	
Fats, &c.	9·2	
Cholesterin	2·6	
Mucus and Pigment	29·8	
Inorganic Salts	7·8	
		140·8

The entire absence of proteids is a marked feature of bile; pancreatic juice, as we shall see, contains a considerable quantity, saliva, as we have seen, a small quantity, normal gastric juice probably still less and bile none at all. Even the bile which has been retained some time in the gall-bladder, though rich in mucus, contains no proteids.

The constituents which form, apart from the mucus, the great bulk of the solids of bile and which deserve chief attention, are the pigments and the bile-salts; of these we shall speak immediately.

With regard to the inorganic salts actually present as such sodium salts are conspicuous, sodium chloride amounting to ·2 or more per cent., sodium phosphate to nearly as much, the rest being earthy phosphates and other matters in small quantity. The presence of iron, to the extent of about ·006 p. c., is interesting, since, as we shall see, there are reasons for thinking that the pigment of bile, itself free from iron, is derived from iron-holding hæmoglobin; some, at least, of the iron set free during the conversion of hæmoglobin into bile pigment, which probably takes place in the liver, finds its way into the bile. Bile also appears to contain a small quantity, at all events occasionally, of other metals, such as manganese and copper; metals introduced into the body are apt to be retained in the liver and eventually leave it by the bile.

The small quantity of fat present consists in part of the complex body lecithin.

The peculiar body *cholesterin*, which though fatty looking (hence the name 'bile fat') is really an alcohol with the composition $C_{26}H_{44}O$, is conspicuous by its quantity and constancy. It forms the greater part of most gall-stones, though some are composed chiefly of pigment. Insoluble in water and cold alcohol, though soluble in hot alcohol and readily soluble in ether, chloroform &c., it is dissolved by the bile-salts in aqueous solution and hence is present in solution in bile. Its physiological functions are obscure.

The ash of bile consists largely of soda, derived partly from the sodium chloride and partly from the bile-salts, of sulphates derived chiefly if not wholly from the latter, and of phosphates partly ready formed, and in part derived from the lecithin.

§ **245**. *Pigments of Bile.* The natural golden red colour of normal human or carnivorous bile, is due to the presence of *Bilirubin.* This, which is also the chief pigmentary constituent of gall-stones, and occurs largely in the urine of jaundice, may be obtained in the form either of an orange-coloured amorphous powder, or of well-formed rhombic tablets and prisms. Insoluble in water, and but little soluble in ether and alcohol, it is readily soluble in chloroform, and in alkaline fluids. Its composition is $C_{16}H_{18}N_2O_3$. Treated with oxidizing agents, such as nitric acid yellow with nitrous acid, it displays a succession of colours in the order of the spectrum. The yellowish golden red becomes green, this a greenish blue, then blue, next violet, afterwards a dirty red, and finally a pale yellow. This characteristic reaction of bilirubin is the basis of the so-called Gmelin's test for bile-pigments. Each of these stages represents a distinct pigmentary substance. An alkaline solution of bilirubin, exposed in a shallow vessel to the action of the air, turns green, becoming converted into *Biliverdin* ($C_{16}H_{20}N_2O_5$ or $C_{16}H_{18}N_2O_4$ Maly), the green pigment of herbivorous bile. Biliverdin is also found at times in the urine of jaundice, and is probably the body which gives to bile which has been exposed to the action of gastric juice, as in biliary vomits, its characteristic green hue. It is the first stage of the oxidation of bilirubin in Gmelin's test. Treated with oxidizing agents biliverdin runs through the same series of colours as bilirubin, with the exception of the initial golden red.

§ **246**. *The Bile-salts.* These consist, in man and many animals, of *sodium glycocholate* and *taurocholate,* the proportion of the two varying in different animals. In man both the total quantity of bile-salts and the proportion of the one bile-salt to the other seem to vary a good deal, but the glycocholate is said to be always the more abundant. In ox-gall, sodium glycocholate is abundant, and taurocholate scanty. The bile-salts of the dog, cat, bear, and other carnivora, consist exclusively of the latter.

Insoluble in ether but soluble in alcohol and in water, the aqueous solutions having a decided alkaline reaction, both salts may be obtained by crystallisation in fine acicular needles. They are exceedingly deliquescent. The solutions of both acids have a dextro-rotatory action on polarized light.

Preparation. Bile, mixed with animal charcoal, is evaporated to dryness and extracted with alcohol. If not colourless, the alcoholic filtrate must be further decolorized with animal charcoal, and the alcohol distilled off. The dry residue is treated with absolute alcohol, and to the alcoholic filtrate anhydrous ether is added as long as any precipitate is formed. On standing the cloudy precipitate becomes transformed into a crystalline mass at the bottom of the vessel. If the alcohol be not absolute, the crystals are very apt to be changed into a thick syrupy fluid. This mass of crystals has been often spoken of as *bilin.* Both salts are thus precipitated, so that in such a bile as that of the ox or man bilin consists both of sodium glycocholate and sodium taurocholate. The two may be separated by precipitation from their aqueous solutions with sugar of lead, which throws down the former much more readily than the latter. The acids may be separated from their respective salts by dilute sulphuric acid, or by the action of lead-acetate and sulphydric acid.

On boiling with dilute acids (sulphuric, hydrochloric), or caustic potash, or baryta water, glycocholic acid is split up into cholalic (cholic) acid and glycin. Taurocholic acid may similarly be split up into cholalic acid and taurin. Thus

$$\overset{\text{glycocholic acid}}{C_{26}H_{43}NO_6} + H_2O = \overset{\text{cholalic acid}}{C_{24}H_{40}O_5} + \overset{\text{glycin}}{CH_2 . NH_2 (CO . OH)}$$

$$\overset{\text{taurocholic acid}}{C_{26}H_{45}NSO_7} + H_2O = \overset{\text{cholalic acid}}{C_{24}H_{40}O_5} + \overset{\text{taurin}}{C_2H_4 . NH_2 . SO_3H}.$$

Both acids contain the same non-nitrogenous acid, cholalic acid; but this acid is in the first case associated or conjugated with the important nitrogenous body glycin, or amido-acetic acid, which is a compound formed from ammonia and one of the "fatty acid" series, viz. acetic; and in the second case with taurin, or amido-isethionic acid, that is a compound into which representatives of ammonia, of the ethyl group, and of sulphuric acid enter. The decomposition of the bile acids into cholalic acid and taurin or glycin respectively takes place naturally in the intestine, the glycin and taurin being probably absorbed, so that from the two acids, after they have served their purpose in digestion, the two ammonia compounds are returned into the blood. Each of the two acids, or cholalic acid alone, when treated with sulphuric acid and cane-sugar, gives a magnificent purple colour (Pettenkofer's test) with a characteristic spectrum. A similar colour may however often be produced by the action of the same bodies on albumin, amyl alcohol, and some other organic bodies.

§ **247**. *Action of Bile on Food.* In some animals at least bile contains a ferment capable of converting starch into sugar; but its action in this respect is wholly subordinate.

On proteids bile has no direct digestive action whatever, but being, generally at least, alkaline, and often strongly so, tends to neutralise the acid contents of the stomach as they pass into the duodenum and as we shall see so prepares the way for the action of the pancreatic juice. To peptic action it is distinctly antagonistic; the presence of a sufficient quantity of bile renders gastric juice inert towards proteids. Moreover when bile, or a solution of bile-salts, is added to a fluid containing the products of gastric digestion, a precipitate takes place, consisting of parapeptone (when present), peptone, pepsin and bile salts. The precipitate is redissolved in an excess of bile or solution of bile-salts; but the pepsin though redissolved remains inert towards proteids. This precipitation actually does take place in the duodenum, and we shall speak of it again later on.

With regard to the action of bile on fats, the following statements may be made:

Bile has a slight solvent action on fats, as seen in its use by painters. It has by itself a slight but only slight emulsifying power: a mixture of oil and bile separate after shaking rather less rapidly than a mixture of oil and water. With fatty acids bile forms soaps. It is moreover a solvent of solid soaps, and it would appear that the emulsion of fats is under certain circumstances at all events facilitated by the presence of soaps in solution. Hence bile is probably of much greater use as an emulsion agent when mixed with pancreatic juice than when acting by itself alone. To this point we shall return. Lastly, the passage of fats through membranes is assisted by wetting the membranes with bile, or with a solution of bile-salts. Oil will pass to a certain extent through a filter-paper kept wet with a solution of bile-salts, whereas it will not pass or passes with extreme difficulty through one kept constantly wet with distilled water.

Bile possesses some antiseptic qualities. Out of the body its presence hinders various putrefactive processes; and when it is prevented from flowing into the alimentary canal, the contents of the intestine undergo changes different from those which take place under normal conditions, and leading to the appearance of various products, especially of ill-smelling gases.

These various actions of bile seem to be dependent on the bile salts and not on the pigmentary or other constituents.

Pancreatic Juice.

§ **248.** Natural healthy pancreatic juice obtained by means of a temporary pancreatic fistula differs from the digestive juices of which we have already spoken, in the comparatively large quantity of proteids which it contains. Its composition varies according to the rate of secretion, for, with the more rapid flow, the increase of total solids does not keep pace with that of the water, though the ash remains remarkably constant.

By an incision through the linea alba the pancreatic duct (or ducts) can easily be found either in the rabbit or in the dog, and a cannula secured in it. There is no difficulty about a temporary fistula; but with permanent fistulæ the secretion is apt to become altered in nature, and to lose many of its characteristic properties. Some, however, have succeeded in obtaining permanent fistulæ without any impairment of the secretion.

Healthy pancreatic juice is a clear, somewhat viscid fluid, frothing when shaken. It has a very decided alkaline reaction, and contains few or no structural constituents.

The average amount of solids in the pancreatic juice (of the dog) obtained from a temporary fistula is about 8 to 10 p. c.; but in even thoroughly active juice obtained from a permanent fistula, is not more than about 2 to 5 p.c., ·8 being inorganic matter; and this is probably the normal amount. The important constituents of quite fresh juice are albumin, a peculiar form of proteid allied to myosin, giving rise to a sort of clotting, a small amount of fats and soaps, and a comparatively large quantity of sodium carbonate, to which the alkaline reaction of the juice is due, and which seems to be peculiarly associated with the proteids.

Since, as we shall presently see, pancreatic juice contains a ferment acting energetically on proteid matters in an alkaline medium, it rapidly digests its own proteid constituents, and, when kept, speedily changes in character. The myosin-like clot is dissolved, and the juice soon contains a peculiar form of alkali-albumin (precipitable by saturation with magnesium sulphate) as well as small quantities of leucin, tyrosin and peptone, which seem to be the products of self-digestion and are entirely absent from the perfectly fresh juice.

§ **249**. *Action on Food-stuffs.* On *starch*, pancreatic juice acts with great energy, rapidly converting it into sugar (chiefly maltose). All that has been said in this respect concerning saliva might be repeated in the case of pancreatic juice, except that the activity of the latter is far greater than that of the former. Pancreatic juice and the aqueous infusion of the gland are always capable of converting starch into sugar, whether the animal from which they were taken be starving or well fed. From the juice, or, by the glycerine method, from the gland itself, an amylolytic ferment may be approximately isolated.

On *proteids* pancreatic juice also exercises a solvent action, so far similar to that of gastric juice that by it proteids are converted into peptone. If a few shreds of fibrin are thrown into a small quantity of pancreatic juice, they speedily disappear, especially at a temperature of 35° C., and the mixture is found to contain peptone. The activity of the juice in thus converting proteids into peptone is favoured by increase of temperature up to 40° or thereabouts, and hindered by low temperatures; it is permanently destroyed by boiling. The digestive powers of the juice in fact depend, like those of gastric juice, on the presence of a ferment which, as we have already said, may be isolated much in the same way as pepsin is isolated, and to which the name *trypsin* has been given.

The appearance of fibrin undergoing pancreatic digestion is however different from that undergoing peptic digestion. In the former case the fibrin does not swell up, but remains as opaque as before, and appears to suffer corrosion rather than solution. But there is a still more important distinction between pancreatic and peptic digestion of proteids. Peptic digestion is essentially an acid digestion; we have seen that the action only takes place in the presence of an acid, and is arrested by neutralisation. Pancreatic digestion, on the other hand, may be regarded as an alkaline digestion; the action is most energetic when some alkali is present; and the activity of an alkaline juice is hindered or delayed by neutralisation and arrested by acidification at least with mineral acids. The glycerine extract of pancreas is under all circumstances as inert in the presence of free mineral acid as that of the stomach in the presence of alkalis. If the digestive mixture be supplied with sodium carbonate to the extent of 1 p.c., digestion proceeds rapidly, just as does a peptic mixture when acidulated with hydrochloric acid to the extent of ·2 p.c. Sodium carbonate of 1 p.c. seems in fact to play in tryptic digestion a part altogether comparable to that of hydrochloric acid of ·2 p.c. in gastric digestion. And just as pepsin is rapidly destroyed by being heated to about 40° with a 1 p.c. solution of sodium carbonate, so trypsin is rapidly destroyed by being similarly heated with dilute hydrochloric acid of ·2 p.c. Alkaline bile, which arrests peptic digestion, seems, if anything, favourable to tryptic digestion.

Corresponding to this difference in the helpmate of the ferment, there is in the two cases a difference in the nature of the products. In both cases peptone is produced, and such differences as can be detected between pancreatic and gastric peptones are relatively small; but in pancreatic digestion the bye-product is not, as in gastric digestion, a kind of acid-albumin, but, as might be expected, a body having more analogy with alkali-albumin. Moreover, before the alkali-albumin is actually formed, the fibrin becomes altered and takes on characters intermediate between those of alkali-albumin and of ordinary albumin; and when fresh raw, *i.e.* unboiled, fibrin is acted upon by pancreatic juice, one or more globulins appear as initial products.

Further, there are evidences that differences, of even a more profound nature than the above, exist between pancreatic and gastric digestion. One of these is the appearance, in the pancreatic digestion of proteids, of two remarkable nitrogenous crystalline bodies, *leucin* and *tyrosin.* When fibrin (or other proteid) is submitted to the action of pancreatic juice, the amount of peptone which can be recovered from the mixture falls far short of the original amount of proteids, much more so than in the case of gastric juice; and the longer the digestive action, the greater is this apparent loss. If a pancreatic digestion mixture be freed from the alkali-albumin by neutralisation and filtration, the filtrate yields, when concentrated by evaporation, a crop of crystals of tyrosin. If these be removed the peptone may be precipitated from the concentrated filtrate by the addition of a large excess of alcohol and separated by filtration. The second filtrate upon being concentrated by evaporation yields abundant crystals of leucin and traces of tyrosin. Thus by the action of the pancreatic juice a considerable amount of the proteid, which is being digested, is so broken up as to give rise to products which are no longer proteid in nature. From this breaking up of the proteid there arise leucin, tyrosin, and probably several other bodies, such as fatty acids and volatile substances.

As is well known, leucin and tyrosin are the bodies which make their appearance when proteids or gelatin are acted on by dilute acids, alkalis, or various oxidising agents. Leucin is a body, which in an impure state crystallizes in minute round lumps with an obscure radiate striation, but when pure, forms thin glittering flat crystals. It has the formula $C_6H_{13}NO_2$ or $C_5H_{10}.NH_2\ (CO.OH)$ and is amido-caproic acid. Now caproic acid is one of the "fatty acid" series, so that leucin may be regarded as a compound of ammonia with a fatty acid. Tyrosin, $C_9H_{11}NO_3$, on the other hand, belongs to the "aromatic" series; it is a phenyl compound, and hence allied to benzoic acid and hippuric acid. So that in pancreatic digestion the large complex proteid molecule is split up into fatty acid and aromatic molecules, some other bodies of less importance making their appearance at the same time. We infer that the proteid molecules are in some way built up out of "fatty acid" and "aromatic" molecules, together with other components, and we shall later on see additional reasons for this view.

Among the supplementary products of pancreatic digestion may be mentioned the body *indol* (C_8H_7N), to which apparently the strong and peculiarly fæcal odour which sometimes makes its appearance during pancreatic digestion is due. Indol, however, unlike the leucin and tyrosin, is not a product of pure pancreatic digestion, but of an accompanying decomposition due to the action of organised ferments. A pancreatic digestive mixture soon becomes swarming with bacteria, in spite of ordinary precautions, when natural juice or an infusion of the gland is used. When isolated ferment is used, and atmospheric germs are excluded, or when pancreatic digestion is carried on in the presence of salicylic acid, or thymol, which prevent the development of bacteria and like organisms but permit the action of the trypsin, no odour is perceived, and no indol is produced.

After long-continued digestion, especially when accompanied by putrefactive decomposition, the amount of proteids which are carried beyond the peptone stage and broken up, may be very great.

In gastric digestion such a profound destruction of proteid material occurs to a much less extent or not at all; neither leucin nor tyrosin can at present be considered as natural products of the action of pepsin.

On the gelatiniferous elements of the tissues as they actually exist in the tissue previous to any treatment pancreatic juice appears to have no solvent action. The fibrillæ and bundles of fibrillæ of ordinary untouched connective-tissue are not digested by pancreatic juice, which in this respect affords a striking contrast to gastric juice. But when they have been previously treated with acid or boiled so as to become converted into actual gelatine, trypsin is able to dissolve them, apparently changing them much in the same way as does pepsin. Trypsin unlike pepsin, will dissolve mucin. Like pepsin, it is inert towards nuclein, horny tissues, and the so-called amyloid matter.

On *fats* pancreatic juice has a twofold action. In the first place it emulsifies fats. If hog's lard be gently heated until it melts and be then mixed with pancreatic juice before it solidifies on cooling, a creamy emulsion, lasting for almost an indefinite time, is formed. So also when olive oil is shaken up with pancreatic juice, the separation of the two fluids takes place very slowly, and a drop of the mixture under the microscope shews that the division of the fat is very minute. An alkaline aqueous infusion of the gland has similar emulsifying powers. In the second place pancreatic juice splits up neutral fats into their respective acids and glycerine. Thus palmitin (or tripalmitin) $(C_{15}H_{31} . CO . O)_3 . C_3H_5$ is with the assumption of $3H_2O$ split up into three molecules of palmitic acid $3(C_{15}H_{31}.CO.OH)$ and one of glycerine $(C_3H_5)(OH)_3$; and so with the other neutral fats. If perfectly neutral fat be treated with pancreatic juice, especially at the body-temperature, the emulsion which is formed speedily takes on an acid reaction, and by appropriate means not only the corresponding fatty acids but glycerine may be obtained from the mixture. When alkali is present, the fatty acids thus set free form their corresponding soaps. Pancreatic juice contains fats, and is consequently apt after collection to have its alkalinity reduced; and an aqueous infusion of a pancreatic gland (which always contains a considerable amount of fat) very speedily becomes acid.

Thus pancreatic juice is remarkable for the power it possesses of acting on all the food-stuffs, on starch, fats and proteids.

The action on starch, the action on proteids, and the splitting up of neutral fats appear to be due to the presence of three distinct ferments, and methods have been suggested for isolating them. The emulsifying power, on the other hand, is connected with the general composition of the juice (or of the aqueous infusion of the gland), being probably in large measure dependent on the alkali and the alkali-albumin present. The proteolytic ferment trypsin as ordinarily prepared seems to be proteid in nature and capable of giving rise, by digestion, to peptone; but it may be doubted, as in the case of pepsin and other ferments, whether the pure ferment has yet been isolated. There are no means of distinguishing the amylolytic ferment of the pancreas from ptyalin. The term *pan-*

creatin has been variously applied to many different preparations from the gland, and its use had perhaps better be avoided.

The action of pancreatic juice, or of the infusion or extract of the gland, on starch, is seen under all circumstances, whether the animal be fasting or not. The same may probably be said of the action on fats. On proteids the natural juice, when secreted in a normal state, is always active. The glycerine extract or aqueous infusion of the gland, on the contrary, as we have already explained, § 237, is active in proportion as the trypsinogen has been converted into trypsin.

Succus Entericus.

§ **250**. When, in a living animal, a portion of the small intestine is ligatured, so that the secretions coming down from above cannot enter its canal, while yet the blood-supply is maintained as usual, a small amount of secretion collects in its interior. This is spoken of as the *succus entericus*, and is supposed to be furnished by the glands of Lieberkühn, of which we shall presently speak.

Succus entericus may be obtained by the following method, known as that of Thiry modified by Vella. The small intestine is divided in two places at some distance (30 to 50 cm.) apart. By fine sutures the lower end of the upper section is carefully united with the upper end of the lower section, thus as it were cutting out a whole piece of the small intestine from the alimentary tract. In successful cases, union between the cut surfaces takes place, and a shortened but otherwise satisfactory canal is re-established. Of the isolated piece the two ends are separately brought through incisions in the abdominal wall and their mouths carefully fastened in such a manner that each mouth of the piece opens on to the exterior. During the process of healing two fistulæ are thus established, one leading to the beginning of and the other to the end of a short piece of intestine quite isolated from the rest of the alimentary canal; by means of these openings a small quantity of fluid can be obtained.

The quantity secreted is said to be considerably increased by the administration of pilocarpin.

Succus entericus obtained from the dog by the above method is a clear yellowish fluid having a faintly alkaline reaction and containing a certain quantity of mucus. It is said to convert starch into sugar, and proteids into peptone (the action being very similar to that of pancreatic juice), to split up neutral fats, to emulsify fats and to curdle milk. It is also said to convert rapidly cane-sugar into grape-sugar, and by a fermentative action to convert cane-sugar into lactic acid, and this again into butyric acid with the evolution of carbonic acid and free hydrogen.

According to the above results, succus entericus is to be regarded as an important secretion acting on all kinds of food.

But even at the best, its actions are slow and feeble. Moreover many observers have obtained negative results, so that the various statements are conflicting. Besides, we have no exact knowledge as to the amount to which such a secretion takes place under normal circumstances in the living body. We may therefore conclude that, at present at all events, we have no satisfactory reasons for supposing that the actual digestion of food in the intestine is, to any great extent, aided by such a juice.

Of the possible action of other secretions of the alimentary canal, as of the cæcum and large intestine, we shall speak when we come to consider the changes in the alimentary canal.

§ **251**. *Gallstones.* Concretions, often of considerable size, known as gallstones are not unfrequently formed in the gall bladder, and smaller concretions are sometimes formed in the bile passages. In man two kinds of gallstones are common. One kind consists almost entirely of cholesterin, sometimes nearly free from any admixture with pigment, sometimes more or less discoloured with pigment. Gallstones of this kind have a crystalline structure, and when broken or cut shew frequently radiate and concentric markings. The other kind consists chiefly of bilirubin in combination with calcium. Gallstones of this kind are dark coloured and amorphous. Less common than the above are small dark coloured stones, having often a mulberry shape, consisting not of bilirubin itself, but of one or other derivative of bilirubin. Gallstones consisting almost entirely of inorganic salts, calcic carbonates and phosphates, are also occasionally met with. In the lower animals, in oxen for instance, bilirubin gallstones are not uncommon, but cholesterin gallstones are rare.

A gallstone appears always to contain a more or less obvious 'nucleus,' around which the material of the stone has been deposited, and which may be regarded as the origin of the stone; the real cause of the formation of the stone lies however in certain changes in the bile, by which the cholesterin, or bilirubin, or other constituent ceases to remain dissolved in the bile. But we cannot discuss this matter here.

SEC. 5. THE SECRETION OF PANCREATIC JUICE AND OF BILE.

§ **252**. *The Secretion of Pancreatic Juice.* Although in some cases, as that of the parotid of the sheep, the flow of saliva is continuous or nearly so, in most animals, as in man, the intermittence of the secretion is very nearly absolute. While food is in the mouth saliva flows freely, but between meals only just sufficient is secreted to keep the mouth moist, and probably the greater part of this is supplied not by the larger salivary but by the small buccal glands. The flow of pancreatic juice, on the other hand, is much more prolonged, being in the rabbit continuous, and in the dog lasting for twenty hours after food. But this contrast between the secretion of saliva and that of pancreatic juice is natural, since the stay of food in the mouth even during a protracted feast is relatively short, whereas the time during which the material of a meal is able in some way or other to affect the pancreas is very prolonged.

The flow though continuous, or nearly so, is not uniform. In the dog the flow of pancreatic juice begins immediately after food has been taken, and rises to a maximum which may be reached within the first, or as in the case furnishing the diagram given in Fig. 69 the second hour, but which more commonly is not reached until the third or fourth hour. This rise is then followed by a fall, after which there is a secondary rise, reaching a second maximum at a very variable time but generally between the fifth and seventh hours. This second maximum, however, is never so high as the first.

The second rise may be due to material absorbed from the intestines being carried in the circulation to the pancreas and so directly exciting the gland to activity, much in the same way as, in the case of the stomach, the absorption of digested material promotes the flow of gastric juice, see § 232; and a similar absorption may contribute to the first rise also, but it is more probable that so marked and sudden a rise as this is carried out by some nervous mechanism. The details of this mechanism have however not as yet been satisfactorily worked out.

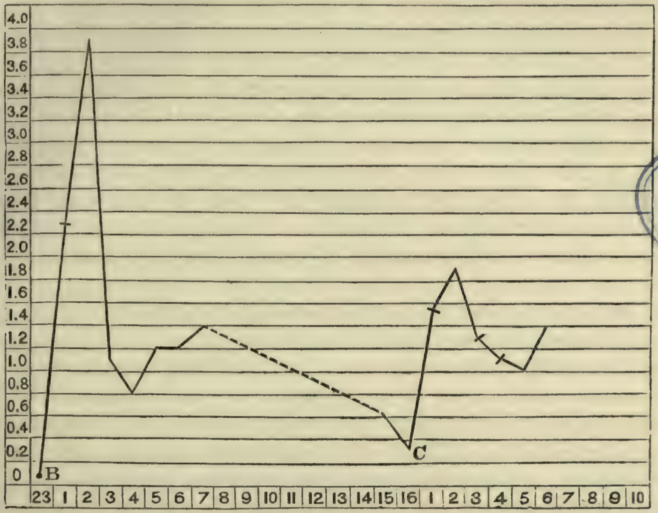

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Fig. 69. Diagram illustrating the influence of Food on the Secretion of Pancreatic Juice. (N. O. Bernstein.)

The abscissæ represent hours after taking food; the ordinates represent in c.c. the amount of secretion in 10 min. A marked rise is seen at B immediately after food was taken, with a secondary rise between the 4th and 5th hours afterwards. Where the line is dotted the observation was interrupted. On food being again given at C, another rise is seen, followed in turn by a depression and a secondary rise at the 5th hour. A very similar curve would represent the secretion of bile.

The pancreas derives its nerves, which reach it along its blood vessels, from the solar plexus of the splanchnic system, but the ultimate origins of the fibres have not been traced out; some of them however certainly come through the plexus from the right vagus.

Stimulation of the medulla oblongata, or of the spinal cord, will call forth secretion in a quiescent gland, or increase a secretion already going on. From this we may infer the existence of a reflex mechanism, though we cannot as yet trace out satisfactorily the exact path of either the afferent or the efferent impulses; all we can say is that the latter do not reach the pancreas by the vagus, since stimulation of the medulla is effective after section of both vagi.

A secretion already going on may be arrested by stimulation of the central end of the vagus, and the stoppage of the secretion which has been observed as occurring during and after vomiting is probably brought about in this way. This effect, which however is not confined to the vagus, stimulation of other afferent nerves, such as the sciatic, producing the same effect, may be regarded (in the absence of any proof that the result is due to reflex constriction of the pancreatic blood vessels unduly checking the blood-supply) as an inhibition of a reflex mechanism at its centre in the medulla or in some other part of the central nervous system, much in the same way as fear inhibits at the central nervous system the secretion of saliva following food in the mouth, § 226. But if so, then we must regard the secretion of pancreatic juice as closely resembling that of saliva in as much as it is called forth by a reflex act. Yet it is stated that, unlike the case of saliva, the secretion of pancreatic juice continues after all the nerves going to the gland have been divided, an operation which would do away with the possibility of reflex action. Such an experiment however cannot be regarded as decisive, since it is almost impossible to be sure of dividing all the nerves.

No evidence has yet been brought forward to prove the existence of any double nervous mechanism similar to that of chorda fibres and sympathetic fibres in the salivary gland. All that can be said is that, when the gland is stimulated to secrete, the blood vessels are dilated as in the salivary gland; and we have already, § 232, dwelt on the histological changes which accompany secretion. We may add that when the gland is stimulated to increased secretion the increase is not merely an increase of water, the discharge of solids is increased even more than the discharge of water, so that the percentage of solids in the juice increases.

The quantity of pancreatic juice secreted, in the case of man, in 24 hours has been calculated at 300 c.c., but such a calculation is of very uncertain value.

We have seen, § 227, that in the salivary glands the pressure which may be exerted by the fluid in the ducts is very considerable, exceeding it may be even the blood-pressure in the carotid artery. In this respect the pancreas differs from the salivary glands. When, in a rabbit, a cannula connected with a vertical tube or a manometer is placed in the pancreatic duct, the column of fluid does not rise above a height corresponding to a pressure of about 17 mm. of mercury. But at this pressure the gland becomes œdematous on account of the juice secreted passing back through the walls of the ducts and alveoli into the connective tissue; a much higher pressure is needed to render a salivary gland œdematous; and whether the low pressure observed in the pancreas is due to the ease with which œdema takes place or to the actual secretion not being able to reach a higher pressure cannot be stated with certainty.

§ 252.* *The Secretion of Bile.* The act of secretion of bile by the liver must not be confounded with the discharge of bile from the bile-duct into the duodenum. When the acid contents of the stomach are poured over the orifice of the biliary duct, a gush of bile takes place. Indeed, stimulation of this region of the duodenum with a dilute acid at once calls forth a flow, though alkaline fluids so applied have little or no effect. When no such acid fluid is passing into the duodenum no bile is, under normal circumstances, discharged into the intestine. The discharge is due to a contraction of the muscular walls of the gall-bladder and ducts, accompanied by a relaxation of the sphincter of the orifice; both acts are probably of a reflex nature, but the details of the mechanism have not been worked out.

The secretion of bile on the other hand, as shewn by the results of biliary fistulæ, is continuous; it appears never to cease. When no food is taken the bile passes from the liver along the hepatic and then back along the cystic duct (the flow being aided probably by peristaltic contractions of the muscular fibres of the duct) to the gall-bladder, where it is temporarily stored; hence in starving animals, when no discharge is excited by food, the gall-bladder becomes greatly distended with bile. But the secretion, though continuous, is not uniform. The rate of secretion varies, and is especially influenced by food; it is seen to rise rapidly after meals, reaching its maximum, in dogs, in from four to eight hours. There seems to be an immediate, sudden rise when food is taken, then a fall, followed subsequently by a more gradual rise up to the maximum, and ending in a final fall to the lowest point. The curve of secretion, in fact, resembles that of the secretion of pancreatic juice in having a double rise; and as in that case so in this, it is very probable that the first rise is in part the result of nervous action, and it is also possible that nervous influences intervene in the second more lasting rise; but, as we shall see presently, even nervous influences may affect the liver in a very indirect manner, and our knowledge as to any direct action of the nervous system on the liver is at present very imperfect.

The liver receives its chief nervous supply from the solar plexus, and to a great extent through that part of the solar plexus called the hepatic plexus which embraces the portal vein, hepatic artery and bile duct, as these plunge into the liver at the porta. The solar plexus is fed by the two abdominal splanchnic nerves, major and minor, by other smaller nerves from the lower parts of the splanchnic (sympathetic) chain, and by the terminal portion of the right vagus nerve. Small branches from the left vagus, rami hepatici, also pass directly to the liver from the terminations of that nerve on the stomach, finding their way also through the porta. The fibres thus entering the liver from the several sources are, for the most part, non-medullated fibres; with these, however, are mixed a certain number of medullated fibres.

As to the functions of these nerves in reference to the secretion of bile, we may say at once that no satisfactory or exact statement can at present be made.

§ **253**. It must be remembered, however, that the liver is so peculiarly related to the other organs of digestion, and its vascular arrangements so special that, with regard to it, as compared with many other organs, an intrinsic nervous mechanism must occupy a more or less subordinate position. The blood-supply of the pancreas for instance is dependent chiefly on the width for the time being of the pancreatic arteries; it will be affected of course by the general arterial pressure and by any circumstances which affect the outflow by the pancreatic veins, and therefore by the condition of the portal venous system of which those veins form a part; but in the main, the amount of blood bathing the alveoli of the pancreas will depend on whether the pancreatic arteries are constricted or dilated. The quality of the blood reaching the pancreas, being arterial blood drawn direct from the arterial foundation, will be modified only by such circumstances as modify the general mass of the blood.

Very different is the case of the liver. The supply of arterial blood coming direct through the hepatic artery is small compared with the mass pouring through the vena portæ; it moreover, as we shall see, is distributed in capillaries among the small interlobular branches of the vena portæ and has become venous, indeed merged with the portal blood, before it reaches the actual lobules. The supply of blood for the liver is mainly that through the vena portæ; and this supply is not, like an arterial supply, a fairly uniform one, modified chiefly by the vaso-motor events of the organ itself, but is dependent on what happens to be taking place in the alimentary canal and in abdominal organs other than the liver itself. When no food is being digested and the alimentary canal is at rest, the vessels of that canal, as we have already said in speaking of the stomach, are like those of the pancreas and salivary glands, in a state of tonic constriction; a relatively small quantity of blood passes through them; hence the flow through the vena portæ is relatively inconsiderable, and the pressure in that vessel is low. When digestion is going on all the minute arteries of the stomach, intestine, spleen and pancreas are dilated, and general arterial pressure being by some means or other maintained (see § 194), a relatively large quantity of blood rushes into the vena portæ and the pressure in that vessel becomes much increased, though of course remaining lower than the general arterial pressure. Moreover during digestion, peristaltic movements of the muscular coats of the alimentary canal are, as we have seen, active; and these movements, serving as aids to the circulation (see § 121), help to increase the portal flow. Further the spleen, as we shall see in speaking of that organ, is in many animals richly provided with plain muscular fibres, and in such cases seems, especially during digestion, to act as a muscular pump driving the blood onwards, with increased vigour, along the splenic veins to the liver. So that even were the liver not connected with the central nervous system by a single nervous tie, the tide of blood through the liver would ebb and flow according to the absence or presence of food in the alimentary canal.

An increase of blood-supply does not of course necessarily mean an increase of secretory activity. As we have seen, § 227, in the presence of atropine, the secretion of saliva may stand still in spite of dilated blood vessels and the consequent rush of blood; but we may safely assert that, other things being equal, a fuller blood-supply is favourable to activity. Apparently a mere change in the quantity of blood bathing an alveolus will not start in the cells the changes which constitute the act of secretion, any more than an increase in the blood bathing a muscular fibre will necessarily set going a contraction; but unless there be some counteracting influence at work, a fuller and richer lymph around a cell will naturally lead to the cell taking up more material from the lymph, and so will increase the cell's store of energy. Hence, especially in the hepatic cell, which appears to be always at work, always undergoing metabolism of such a kind as to give rise to bile, we might fairly expect the greater flow through the portal vein to quicken the flow through the bile duct.

And as a matter of fact we do find vaso-constrictor action dominant over the secretion. In the various experiments which have been made to ascertain the action of the nervous system on the secretion of bile, it has always been found that stimulation of the medulla oblongata, or of the spinal cord, or of the abdominal splanchnic nerves, stops or at least checks the flow of bile. Now the effect of these stimulations is, as we have already seen more than once, a powerful constricting action on the abdominal blood vessels; by such stimulation the blood-supply of the liver is materially diminished, and in consequence the secretory activity is slackened or arrested.

But there is something besides the mere quantity of blood to be considered in this relation. The blood which passes from the alimentary canal at rest is ordinary venous blood, laden simply with carbonic acid and the ordinary products of the metabolism of the muscular and mucous coats of the canal. When digestion is going on the portal blood is laden, as we shall see, with some at all events of the products of digestion, with sugar probably and with various proteid bodies. And it is quite possible or even probable that some of these bodies in the portal blood reaching the hepatic cells stir them up to secretory activity; indeed this view may be regarded as supported by the facts that proteid food increases the quantity of bile secreted, whereas fatty food, which as we shall see passes, chiefly if not wholly, not by the portal vein but by the lymphatics and which is probably largely disposed of in some way or other before it can reach the liver, has no such effect.

Hence we may infer that at all events the second increase of the flow of bile which occurs during the later stages of digestion may be to a large extent the direct effect of blood, laden with digestive products, passing from the stomach and intestines, especially the latter, to the liver by the portal vein, quite independent of any direct nervous action on the liver itself; and indeed it is possible that the first rise also may be partly due to the increased flow of blood from the stomach, aided by the absorption from that organ of a certain amount of digested material. Since, however, there is no evidence of any decrease in blood-supply, or in the rate of absorption, corresponding to the fall between the two rises, some influences other than those which we are discussing must be at work in the matter.

§ **254**. The blood-supply of the liver being thus, quite apart from any nervous supply of its own, so closely dependent on what is going on in the alimentary canal, it will be convenient to say a few words more concerning the vaso-motor nerves of that canal. As we have already said in speaking of the vascular system (§ 169), the vaso-constrictor fibres for the stomach and intestines, large and small, issuing from what we may call the vaso-constrictor region of the cord pass for the most part through the two abdominal splanchnic nerves, major and minor, a small number only passing out below the roots of those nerves. When these splanchnic nerves are divided the vessels of the canal are dilated, when they are centrifugally stimulated the vessels are constricted. Whether there be any distinct vaso-dilator fibres for all or any part of the canal, and if so what course they take, is not known. When no food has for some time been taken, the mucous membrane of the stomach as seen through a gastric fistula is pale; the blood vessels are constricted. And as far as we know a similar condition obtains throughout the small and large intestines. When food is taken the mucous membrane of the stomach becomes flushed; its vessels become dilated. This appears to be the result of an inhibition of the previously existing tonic constriction; at least we have no evidence supporting any other explanation. Apparently the presence of food in the stomach starts in the mucous membrane influences which, ascending to the central nervous system, inhibit the vaso-motor centre for the abdominal splanchnic nerves or such part of that centre as governs the vaso-constrictor fibres of the stomach. By what path such afferent impulses reach the central nervous system is not as yet definitely settled; but possibly by the vagus nerve, if it be true, as stated, that centripetal stimulation of that nerve, while it raises the general blood-pressure by increasing, in a reflex manner, vaso-constriction in other regions, leads to a dilation of the gastric vessels. So also it is probable that as the food reaches succeeding sections of the alimentary canal, these in turn in a similar manner become flushed with blood. In the frog there is some evidence that vaso-constrictors leaving the spinal cord by consecutive spinal nerves govern the blood vessels of consecutive sections of the alimentary canal.

All this flushing of the canal with blood leads, we repeat, to an increased flow of blood at a higher pressure through the portal vein. Whether besides this there be any additional mechanism set to work, such as, for instance, which some observations suggest, a rhythmical peristaltic contraction of the portal vein, by which the blood is still more rapidly hurried to the liver, and whether the increased venous supply through the portal vein is accompanied by a corresponding increase of the lesser supply of arterial blood through the hepatic artery, is not known. It may perhaps be here remarked that there is no need for any increase of arterial blood, since the blood from the alimentary canal, owing to its more rapid passage through the minute vessels, is probably like the corresponding blood in the veins of an active salivary gland, (though probably also not to the same extent) less venous than usual during digestion in spite of the extra quantity of carbonic acid thrown into it by the increased metabolism of the muscular coat during the peristaltic movements.

§ **255**. It is interesting to observe that the pressure under which the bile is secreted is relatively low like that of the pancreatic juice, not high like that of the saliva; it is much lower than the arterial pressure in the same animal, whereas in the case of saliva (§ 227) the pressure is greater than the blood-pressure in the carotid artery. But, in the case of bile, since the blood which flows through the hepatic lobules is, mainly, venous portal blood, we have to compare the pressure of the secretion not with arterial pressure but with the venous pressure in the portal system; and in the dog it has been found that while the pressure of the bile secreted stood at about 200 mm. of a solution of sodium carbonate, that is, about 15 mm. mercury, the blood-pressure in a branch of the superior mesenteric vein stood only at about 90 mm. of the same solution, that is, about 7 mm. mercury. Now the venous pressure in the mesenteric veins is higher, though only slightly higher, than that in the portal vein into which these pour their blood (the difference of pressure being the main cause why the blood flows from the one into the other), and is therefore certainly higher than the pressure in the portal capillaries of the hepatic lobules. So that what is true of the salivary gland is also true, on a different scale, of the liver, viz. that the pressure exerted by the secretion is higher than the pressure of the blood in the vessels feeding the secreting cells.

§ **256**. If the pressure in the bile duct be artificially increased, as by pouring fluid into the glass tube or manometer with which the cannula in the duct is connected, a resorption of the secreted bile takes place; and resorption will also take place within the body, when the pressure generated by the act of secretion itself reaches and is maintained at a sufficiently high level. Thus when in the living body the bile duct is ligatured, or becomes obstructed by gallstones or otherwise, fluid is accumulated on the near side of the ligature at a pressure which goes on increasing until resorption of bile takes place, bile salts and biliary pigments are thrown back upon the system, and "jaundice" results. It would appear that in these cases resorption takes place through the interlobular bile ducts and not through the hepatic cells or other structures within the lobules. The high pressure in the ducts does not lead to a reversal of the current in the hepatic cells (at most it slackens or possibly stops the current) but the bile secreted into the interlobular ducts escapes from these. It further appears that the escape is not into the blood vessels but into the lymphatics; the bile salts, pigments and other constituents are carried into the thoracic duct, and in an indirect manner only find their way into the blood stream.

To complete the history of the secretion of bile we ought now to turn to the manufacture of the biliary constituents within the cells. But since the hepatic cells are also engaged in labours other and more important perhaps than that of secreting bile, it will be convenient to defer what we have to say on this point until we come to speak of the formation of glycogen and of the general metabolic events taking place in the liver.

SEC. 6. THE STRUCTURE OF THE INTESTINES.

The Small Intestine.

§ **257.** The intestine, small and large, throughout its length from the pylorus to close upon the rectum, follows in its structure the general plan previously described § 208. A thin outer longitudinal muscular layer, covered by peritoneum, is succeeded by a thicker inner circular muscular layer, and this double muscular coat is separated by a submucous layer of loose connective-tissue, carrying the larger blood vessels, from the mucous membrane which consists of an epithelium lying upon a connective-tissue basis of peculiar nature, a well-developed muscularis mucosæ of longitudinal and circular fibres marking off the mucous membrane proper from the underlying submucous tissue.

In the small intestine the outer longitudinal muscular layer is evenly distributed over the whole circumference of the tube and is everywhere much thinner than the inner circular layer, which is the more important layer of the two. The individual fibre-cells of these muscular layers of the intestine are large and well developed. In the thin sheet of connective-tissue which separates indistinctly the two layers lies the plexus of Auerbach, a plexus of nerve-fibres, for the most part non-medullated, at the nodes of which are gathered groups of very small nerve-cells, the substance of each cell being especially scanty. This plexus supplies the two muscular layers with nerve-fibres.

The submucous coat contains besides blood vessels and lymphatics, a somewhat similar plexus of nerve-fibres, called the plexus of Meissner; from this plexus fine nerve-fibres proceed to the blood vessels, to the muscularis mucosæ, and possibly to other structures.

§ **258.** *The Mucous Membrane.* This is thrown into folds which are not as in the case of the stomach temporary longitudinal folds, *rugae*, but permanent transverse folds, the *valvulae conniventes*, reaching half-way or two-thirds of the way round the tube. Each fold is a fold of the whole mucous membrane carrying with it a part of the submucous tissue, the latter thus forming a middle sheet between the mucous membrane on the upper surface and that on the lower surface of the fold. The folds, which vary in size, large and small frequently alternately, begin to appear at a little distance from the pylorus; they are especially well developed just below the opening of the bile and pancreatic ducts, and are continued down to about the middle of the ileum, where, becoming smaller and irregular, they gradually disappear. They serve to increase the inner surface of the intestine and present an obstacle to the too rapid transit of material along the tube.

Over and above the coarser inequalities of surface caused by these folds, the level of the mucous membrane is broken on the one hand by tongue-like projections, the *villi*, and on the other hand by tubular depressions, the *glands* or *crypts* of *Lieberkühn*. The latter are very much smaller and are more numerous than the former, several crypts being placed in the interval between two villi. Both are found on the projecting valvulæ as well as in the valleys between, and both extend along the whole length of the intestine from the pylorus to the ileocæcal valve; but while the villi vary a good deal, being short and few immediately next to the pylorus, very numerous and large in the duodenum and upper part of the intestine, less numerous, smaller, and more irregular in the lower part, the crypts have nearly the same characters and are uniformly distributed throughout. Very much as in the case of the stomach, the muscularis mucosæ runs in an even line (except for the sweeps of the valvulæ conniventes) at a little distance from the bases of the closely packed crypts, and at a greater distance (viz. the length of the crypts) from the bases of the villi; as we shall see, however, the muscularis mucosæ sends up muscular fibres into each villus.

§ **259**. Before proceeding to describe the villi and crypts it will be convenient to study the characters of the peculiar connective-tissue lying between the epithelium above and the muscularis mucosae below. The upper surface of this tissue is defined by what may be spoken of as a basement membrane, which however appears not to be here (at least over the villi) as in the stomach a continuous sheet composed of flat connective-tissue corpuscles fused together, but to have a structure which we shall presently describe. The muscularis mucosæ consists of an outer longitudinal and an inner circular sheet of plain muscular fibres, in some places the one, and in other places the other being predominant; each sheet consists in most cases of a single layer of fibres, the constituent fibres being cemented into flat bundles and the bundles united by fine connective-tissue. Between the flat bundles vessels pass to and from the submucous tissue below and the rest of the mucous membrane above, the muscle itself being also well provided with blood vessels.

The connective tissue which occupies the whole of the narrow irregular zone between the basement membrane above and the muscularis mucosæ below, except for the space taken up by the blood vessels and definite lymphatic vessels (of which we shall presently speak), is of a kind, which, though it is not quite the same in the villi as elsewhere, is on the whole closely allied to the kind known under the various names of *retiform* or *reticular* connective tissue, *adenoid* tissue or *lymphoid* tissue, and indeed is often called by one or other of these names.

Typical adenoid tissue such as is met with in the lymphatic follicles of the intestine, of which we shall presently have to speak, in lymphatic glands and elsewhere, presents the appearance of a fine close-set and fairly regular network with meshes so small as not to afford room for more than one or two leucocytes in each mesh. The bars of the network are delicate fibres composed of material which is similar to, if not identical with, that of the fibrillæ of ordinary connective tissue. At the nodal points of the network thickenings are frequently but not always present, and some of the more conspicuous of these thickenings may contain nuclei either spherical in form or more or less misshapen; but such nuclei are not numerous. Adenoid tissue in fact is composed of anastomosing branched cells, the greater part of the cell in most cases, and indeed the whole of the cell in some cases, having been transformed into filamentous processes, of a differentiated nature, which join freely with each other and with the like processes of other cells to form a fine regular network, a portion only of the cell, sometimes with and sometimes without its nucleus (this having disappeared), being left to form a nodal thickening.

It may be regarded as a less developed form of connective-tissue than the white fibrous or the ordinary areolar connective-tissue. In the earlier stage of its development in the embryo connective-tissue of all kinds is represented by a number of nucleated granular protoplasmic cells, lying in a fluid or nearly fluid matrix. The cell-bodies are branched, the branches joining together at intervals to form a network. In the development of ordinary connective-tissue the outer portion of the cell-body of some of the cells is converted into or at least gives rise to fibrillar gelatiniferous material, or the whole of it may be so converted, the rest of the cell, or other cells, being left as connective-tissue corpuscles. In adenoid tissue the cells remain as branched cells, joining into a network, and the cell-substance is not in any part transformed into bundles of fibrillæ, though it has undergone, besides an increase in its branching, in part at all events, a chemical transformation, since the material forming the bars of the network is in a large measure no longer ordinary 'protoplasmic' cell-substance. The meshes of typical adenoid tissue are always crowded with, and practically filled up by, leucocytes of various sizes; it is only with very great difficulty that the network can be obtained free from them.

The connective-tissue occupying the spaces between and below the glands of Lieberkühn is very similar to adenoid tissue in as much as it presents a network of delicate fibres; but the meshes are somewhat larger and more irregular than those of true adenoid tissue, and though they contain, are not crowded with, leucocytes; the amount of cell-substance left at some of the nodal points is greater, nuclei are more abundant, and some of the processes of the cells forming the bars of the network are flat expansions rather than fibres. It is on the whole therefore somewhat different from the typical adenoid tissue of lymphatic structures, and though it is often spoken of under the same name as that tissue, it will be convenient to distinguish it by some term; it might be called *reticular* tissue.

The tissue which fills up the body of a villus differs still more from true adenoid tissue; it is formed of branching cells which have for the most part retained their nuclei and a larger amount of cell-substance round each nucleus; the processes are partly membranous, partly fibres, and some of them exhibit a tendency to form minute bundles of fibrillæ. It is intermediate between adenoid-tissue and ordinary connective-tissue, and may perhaps be described as forming a loose somewhat open sponge-work rather than a network.

Lying loose in the meshes of this peculiar reticular connective-tissue, both in the villi and elsewhere, are seen bodies having the general characters of white blood corpuscles (see § 31), which, though they are probably not all of the same kind, we may speak of under the term of leucocytes. Sometimes these are scanty but often are very numerous. This reticular connective-tissue forms in fact a labyrinth of irregular passages which are occupied by fluid but through which leucocytes can wander to and fro. We shall later on point out that this labyrinth of passages is associated in a particular manner with the lymphatic vessels and that the fluid occupying the spaces is in reality lymph. Indeed this tissue ought perhaps to be regarded as part of the lymphatic system.

The basement membrane spoken of above appears to be formed largely, at least over the villi, by the expanded ends of fibres of the reticulum which reaching the surface from below spread out laterally beneath the epithelium, and being joined by a certain number of cells lying flat on the surface, form together a sheet which is not continuous but discontinuous, being broken by openings through which the bases of the cells of the epithelium are brought into contact with the fluid occupying the spaces of the reticulum below.

§ 260. *The Villi.* The villi vary in size and form in different animals, and in different parts of the intestine in the same animal; each villus moreover varies in form at different times; they may be generally described as having the shape of a flattened finger but are frequently broader at the free end than at the base; they have, in man, a length of about 1 mm. and a breadth of from ·2 mm. to ·5 mm.

Each villus consists of a *body* of reticular tissue, the outer surface forming, as explained above, a basement membrane, which is covered by a single layer of *epithelium cells.* Two kinds of cells, that is cells presenting two sets of characters, make up this single layer of epithelium.

One kind is a columnar or conical cell, with its broader end forming part of the free surface of the villus, and its narrower end resting on or filling up a gap in the basement membrane. The greater part of the cell-body is formed of the kind of 'granular' cell substance spoken of as protoplasmic, but differs in appearance and condition according to circumstances; these variations we shall study separately. An oval nucleus is placed vertically at about the lower third of the cell. At the free border of each cell the granular cell-substance changes to a narrow band of clear hyaline refractive material marked, in many prepared specimens and often even in the fresh state, with fine vertical lines so as to appear striated vertically or rather radially; in a section of a villus, optical or actual, the whole villus seems to be surrounded by a band of this clear refractive material.

A ciliated epithelium bears, as we have seen (§ 93), a similar hyaline refractive border from which the cilia project and with which they are connected, but which does not share in the movements of the cilia belonging to it, remaining unchanged in form while these are moving; its exact nature is at present uncertain. The refractive border of a columnar cell of a villus differs from the similar border of a ciliated cell in that on the one hand it never, in vertebrates, bears cilia, and on the other hand does under certain circumstances change its form. The striation spoken of above appears to be due to the fact that the border is composed of a number of rods imbedded side by side in a substance which is sometimes of the same refractive power as the rods, in which case the whole border appears homogeneous, but which is sometimes of different refractive power, in which case the striation is distinct. The rods, which are thought by some to be hyaline processes of the underlying cell-substance projecting into the above-mentioned cement-substance, are sometimes long and thin, sometimes short and thick, the whole border being in the former case narrow, in the latter broad. Under the influence of reagents or of circumstances the one condition may change into the other, and the change seems to be an active not a passive process, since it will only take place so long as the cells are alive. This refractive border of the columnar cell of a villus is obviously a peculiar and presumably an important structure.

§ **261**. Mixed in varying proportion with the columnar cells possessing this characteristic hyaline border, are cells of another kind, the *goblet cells.* These are essentially mucous cells; in all their important characters they resemble the mucous cells previously described (§ 235), but receive their special name because in shape they usually resemble a goblet or flask. In a hardened and prepared specimen of a villus numerous goblet cells may be seen scattered among and surrounded by columnar cells. Each goblet cell has a base, often irregular and sometimes branched, lying on or near the basement membrane, and a top which reaches the surface of the villus between the refractive borders of the neighbouring columnar cells. Near the base is placed a nucleus, generally disc-shaped, owing to the action of the reagent, surrounded by a small quantity of staining protoplasmic cell-substance. Above this the cell consists of a mass of transparent mucin, lying in the meshes of a delicate reticulum, and surrounded by a thin layer or envelope which is prolonged upwards from the cell-substance below, and which on the top or free surface of the cell usually bears a distinct round orifice or mouth. The upper part of the cell is consequently a sort of cup filled with mucin (and reticulum) and opening into the interior of the intestine by a somewhat narrow mouth, through which the mucin in due time escapes.

In a villus examined quite fresh in normal saline solution some of these goblet cells may be observed in a condition which has been described, § 235, as the normal condition of a mucous cell. The cell is then cylindrical or oval rather than distinctly flask-shaped, and the upper part of the cell consists of cell-substance studded with granules and spherules, the transparent mucin being absent and the mouth not visible. But in perfectly fresh villi, studied under even the most favourable conditions, many if not most of the goblet cells will be seen to have become goblet shaped, to have already undergone the transformation into transparent mucin and reticulum, and to have acquired a mouth. In such cases the clear transparent body of a goblet cell stands out in strong contrast with the more dim granular bodies of the columnar cells which surround it, both when they are seen on their side and when they are looked at from above. In the latter case when the microscope is focussed for a point a little below the free surface of the villus, the goblet cells look like round clear droplets scattered in the dim ground formed by the columnar cells. A similar contrast is afforded by prepared specimens stained with carmine and certain other dyes, which leave the transparent mucin unstained. Under certain methods or conditions of hardening however and with certain dyes, as with haematoxylin, the mucin may stain as deeply or even more deeply than its surroundings.

Obviously these goblet cells are simply mucous cells somewhat modified by reason of their position. They are not hidden in the recesses of an alveolus like salivary mucous cells, they do not form a layer by themselves like the gastric mucous cells, but are scattered among other cells carrying on important functions. Hence apparently their shape of a goblet and their well-defined mouth. A goblet cell to start with is a cell of a more or less columnar form and ordinary protoplasmic cell-substance. The cell-substance manufactures and becomes studded with granules or spherules which very speedily give rise to mucin, the cell swollen with its load assumes a goblet shape, and the formation of a mouth in the space between the converging refractive borders of neighbouring columnar cells assists in the discharge of the load.

The columnar cells of the villus are, as we shall see, chiefly occupied in the reception of material from the intestine into the body of the villus; the goblet cells are chiefly occupied in secreting into the interior of the intestine mucin and possibly some of the constituents of the succus entericus.

Below this layer of columnar and goblet cells extends the thin basement membrane, above which, between the bases of the other cells, may be seen small cells, that is to say, cells with a relatively small quantity of cell-substance round the nucleus; these have been taken to be reserve or replacement cells. But at times clearly recognizable leucocytes may be seen between the columnar cells; these have probably wandered into the epithelium from the body of the villus; and it may be that some of the small cells in question are of an allied nature.

§ **262**. The centre or rather the axis of the body of the villus is occupied by a club-shaped space, sometimes bifurcate or even branched at the distal end, varying indeed a great deal in different animals. This is the central lymphatic space or 'lacteal radicle,' as it has been called, which may be filled with fatty or other material, or, as more frequently is seen in hardened preparations, may be empty and collapsed. It is lined with epithelioid plates, and is at the base of the villus continuous with the lymphatic passages and vessels of the mucous membrane. It will be convenient to defer the further study of this lymphatic space until we come to deal with the lymphatics generally.

Between this lymph-space, and the basement membrane, generally close underneath the latter, lies a fairly close-set network of capillary vessels, especially well developed towards the upper part of the villus. This network is fed by generally one small artery which springing from the arteries of the submucous tissue splits up into capillaries towards the middle of the villus; and the blood of the capillaries passes into veins, generally two, which in a similar manner pass down to the veins of the submucous tissue.

Between the basement membrane and the central lymph-space, are also found a number of plain muscular fibres, some running singly, others forming small bundles of two or three fibres abreast. These vary much in number and disposition in different animals. Some of them lie close under and end in the basement membrane; others lie nearer the lymph-space, to which in some animals they form a sort of muscular sheath. These fibres belong to the muscularis mucosæ; at the base of the villus the fibres of the muscularis mucosæ take an upward course, passing between the adjacent crypts of Lieberkühn, and run into the villus, following most commonly a longitudinal but sometimes a more or less oblique or even a transverse direction. By the contraction of these fibres the form of the villus can be changed; but we shall return to this point when we come to speak of the absorption of digested material by means of the villi.

All the space intervening between the basement membrane and the central lymph-space which is not taken up by the blood vessels and the muscular fibres, is occupied by the special kind of reticular connective-tissue described above (§ 259), the meshes of which are to a greater or less extent occupied by leucocytes. On the outer surface of the body of the villus this reticular tissue is connected with, and indeed as we have seen forms the basement membrane; in the centre it forms around the epithelioid plates of the lymph-space the walls of that cavity, and supplies a similar bed for the blood capillaries; the fine connective tissue belonging to the small bundles of muscular fibres is continuous with it, and some of the muscular fibres seem to end in it; to it also is attached the connective-tissue of the outer walls of the small artery and veins. The body of the villus is in fact a sponge work of reticular tissue in which are excavated the lymph-space and the blood channels with their respective linings, into which the plain muscular fibres plunge, and which is condensed on the outside into a basement membrane. The meshes of the sponge work are further occupied, as we have said, with leucocytes or with nucleated cells of an allied but different nature; hence in ordinary stained specimens, not specially prepared, the lymph-space and blood channels being collapsed, the whole body of the villus appears a confused mass of nuclei; there are the nuclei of the muscular fibres, the nuclei of the epithelioid plates of the lymph-space and capillaries and of the other coats of the artery and veins, the nuclei of the leucocytes in the meshes, and lastly the nuclei belonging to the reticular tissue itself.

The thickness of the body of the villus, that is to say the amount of reticular and of the other tissues lying between the bases of the epithelium cells and the central lymph-space, varies in different animals, being for instance considerable in the dog and small in the rabbit; in the latter animal the muscular fibres are very scanty.

§ 263. *The Crypts or Glands of Lieberkühn.* These are found everywhere along the whole length of the small intestine from the immediate vicinity of the pylorus to the ileocæcal valve, except immediately underneath each villus, and in the spots occupied by the lymphatic follicles of which we shall presently speak. The mucous membrane of the small intestine is in fact to a very large extent made up of a number of these short tubular glands placed side by side and packed closely together, though not so closely as the somewhat similarly arranged cardiac glands of the stomach; these glands form the greater part of the thickness of the intestinal mucous membrane, and the muscularis mucosæ runs in a fairly even line at some little distance below them, that is outside their blind ends. Each gland is a straight or nearly straight tube, rarely dividing, about 400 μ long and 70 μ broad. The outline is furnished by a very distinct basement membrane, in which nuclei are imbedded at intervals, and this basement membrane is lined with a single layer of short cubical cells, leaving a small but distinct lumen; the cells should perhaps be rather described as somewhat conical, with a broader base at the basement membrane and a narrower apex abutting on the lumen. The cell-body, surrounding a somewhat spherical nucleus, is faintly granular except for a hyaline free border, which however is not so conspicuous or so constant as in the columnar cells of the villi. Similar cells cover the ridges intervening between adjacent glands, and where a villus comes next to a gland the short cubical cells of the gland may be traced into the columnar cells of the villus, the hyaline border becoming more marked and the nucleus becoming oval. Among the cubical cells of the gland are to be found, in varying numbers, goblet cells quite similar to those of the villi. It sometimes happens that during the preparation of a specimen the whole epithelium is shed *en masse*, the cells being much more adherent to each other than to the basement membrane; in such a case the features of the basement membrane are well seen.

Outside the basement membrane, between adjacent glands and between the blind ends of the glands and the underlying muscularis mucosæ, is reticular connective-tissue, finer and more truly reticular than that of the villi; it is perhaps less crowded with leucocytes. In this reticular tissue run, encircling the glands, capillary blood vessels supplied by small arteries coming from the submucous tissue, and pouring their blood into corresponding veins, and with this reticular tissue lymphatics are connected.

These glands of Lieberkühn are supposed to furnish the succus entericus. The reasons for this view lie in their tubular form, which is that of many secreting glands, in their lumen being too narrow for the passage of food into it, and in the fact that, as we shall see, they unlike the columnar cells of the villi are not concerned in the absorption of fat; otherwise there are no definite facts to prove that the cubical cells are concerned in secretion only or that they may not absorb matter other than fat. The goblet cells in these glands as in the villi certainly secrete mucus, and may secrete also some of the constituents of the succus entericus.

Besides these glands properly so called, that is to say involutions of the epithelial (hypoblastic) mucous membrane, there are found in the mucous membrane bodies belonging to the lymphatic system also often called glands, viz. the solitary glands and the agminated glands or patches of Peyer. We shall speak of these as lymphatic follicles, and it will be convenient to study them separately in connection with the lymphatic system.

§ **264**. Immediately below the pylorus in man, but varying somewhat in position in different animals, are the glands of Brunner. These may be regarded as modifications of the pyloric glands of the stomach. In each gland a duct, lined with short columnar epithelium cells leaving a distinct lumen, extends single for some distance, and piercing the muscularis mucosæ divides in the submucous tissue into a number of tubes, which subdividing take a twisted course and end in slight enlargements or alveoli. The cells lining both the branching tubes and the alveoli are short cubical cells with an indistinct outline, similar to but, in a fresh condition, more distinctly granular than the cells of the gastric pyloric glands. Bundles of plain muscular fibres, stragglers from the muscularis mucosæ, are scattered among the tubes.

These glands of Brunner when traced back to the stomach are found to pass gradually into the pyloric glands; traced along the intestine they soon disappear, the ducts of those glands which reach into the duodenum so far as to be found in company with the glands of Lieberkühn and villi, open into the lumina of the former.

It is not clear that any special purpose is served by these glands of Brunner; an extract of the glands is said to digest fibrin in the presence of acid.

The Large Intestine.

§ **265**. The general plan of structure of the large intestine is the same as that of the small intestine, the salient points of distinction being the absence of villi, and a peculiar arrangement of the longitudinal coat.

Instead of being uniformly distributed as a thin layer over the whole circumference of the tube as in the small intestine, the longitudinal coat is in the large intestine chiefly gathered up into three thickened bands or bundles, being very thin elsewhere. These bands moreover are shorter than what may be called the natural length of the intestine, so that the tube instead of being as in the small intestine of fairly uniform bore, is puckered up into 'sacculi' more or less divided by the three bands into groups of three. This sacculated arrangement answers much the same purpose as the arrangement of valvulæ conniventes in the small intestine. The circular muscular layer is thicker in the middle or bellies of the sacculi than at the puckers, where it is very thin.

The villi as we have just said are wholly absent. In the lower part of the small intestine they become fewer and smaller, and none at all are found beyond the ileocæcal valve. An increase of surface is provided by longitudinal ridges, but these like the corresponding rugæ of the stomach involve the whole mucous membrane, including part of the submucous tissue.

The glands of Lieberkühn in the large intestine are in the main like those of the small intestine but larger and better developed, being both deeper and broader, and owing to the absence of villi are more easily studied. The cells of the glands have the same characters as in the small intestine except that the hyaline border is rarely present; goblet cells are perhaps more abundant than even in the small intestine, especially in some animals. On the ridges between the glands the cells become longer and thinner, and the hyaline border, frequently striated, makes its appearance. The marked development of these glands in the large intestine is noteworthy since, as we shall see, absorption of material and not the secretion of digestive juice is the characteristic work of the large intestine. It can scarcely be imagined that absorption takes place only at the ridges between the glands and not by the immensely larger amount of surface which is presented by the interiors of all the glands together; but if these glands absorb in the large intestine, they probably act in the same way in the small intestine.

Lymphatic follicles are abundant in the large intestine, the cæcum and especially the appendix vermiformis being crowded with solitary follicles. The patches of Peyer are absent.

§ **266**. *The Rectum.* As the sigmoid flexure passes into the rectum the three bands of the longitudinal muscular coat spread out and become once more a uniform layer; and with this change the sacculation disappears. This longitudinal coat is continued to the anus, where it ends abruptly. The circular coat at its termination at the anus is developed into a distinct ring, the internal sphincter.

The mucous membrane is thrown into numerous folds or ridges which below are longitudinal but higher up oblique or even transverse in direction; to permit the formation of these folds, which are obliterated when the rectum is fully distended, the submucous tissue is more abundant and more loosely developed than in the rest of the intestine.

Down to the margin of the anus the mucous membrane retains the characters of the large intestine, glands being still present; it then abruptly puts on the epiblastic characters of the epidermis. The rectum has a special nervous supply, but of this we shall speak in connection with the movements of the alimentary canal.

SEC. 7. THE MUSCULAR MECHANISMS OF DIGESTION.

§ 267. From its entrance into the mouth until such remnant of it as is undigested leaves the body, the food is continually subjected to movements having for their object the trituration of the food as in mastication, or its more complete mixture with the digestive juices, or its forward progress through the alimentary canal. These various movements may briefly be considered in detail.

Mastication. This in man consists chiefly of an up and down movement of the lower jaw, combined, in the grinding action of the molar teeth, with a certain amount of lateral and fore-and-aft movement. The lower jaw is raised by means of the temporal, masseter, and internal pterygoid muscles. The slighter effort of depression brings into action chiefly the digastric muscle, though the mylohyoid and geniohyoid probably share in the matter. Contraction of the external pterygoids pulls forward the condyles, and thrusts the lower teeth in front of the upper. Contraction of the pterygoids on one side will also throw the teeth on to the opposite side. The lower horizontally placed fibres of the temporal serve to retract the jaw.

During mastication the food is moved to and fro, and rolled about by the movements of the tongue. These are effected by the muscles of that organ governed by the hypoglossal nerve.

The act of mastication is a voluntary one, guided, as are so many voluntary acts, not only by muscular sense but also by contact sensations. The motor fibres of the fifth cranial nerve convey motor impulses from the brain to the above-mentioned muscles; but paralysis of the sensory fibres of the same nerve renders mastication difficult by depriving the will of the aid of the usual sensations.

§ 268. *Deglutition.* The food when sufficiently masticated is, by the movements of the tongue, gathered up into a bolus on the middle of the upper surface of that organ. The front of the tongue being raised—partly by its intrinsic muscles, and partly by the styloglossus—the bolus is thrust back between the tongue and the palate through the anterior pillars of the fauces or isthmus faucium. Immediately before it arrives there, the soft palate is raised by the levator palati, and so brought to touch the posterior wall of the pharynx, which, by the contraction of the upper margin of the superior constrictor of the pharynx, bulges somewhat forward. The elevation of the soft palate causes a distinct rise of pressure in the nasal chambers; this can be shewn by introducing a water manometer into one nostril, and closing the other just previous to swallowing. By the contraction of the palato-pharyngeal muscles which lie in the posterior pillars of the fauces, the curved edges of those pillars are made straight, and thus tend to meet in the middle line, the small gap between them being filled up by the uvula. Through these manœuvres, the entrance into the posterior nares is blocked, while the soft palate is formed into a sloping roof, guiding the bolus down the pharynx. By the contraction of the stylo-pharyngeus and palato-pharyngeus, the funnel-shaped bag of the pharynx is brought up to meet the descending morsel, very much as a glove may be drawn up over the finger.

Meanwhile in the larynx, as shewn by the laryngoscope, the arytenoid cartilages and vocal cords are approximated, the latter being also raised so that they come very near to the false vocal cords; and the cushion at the base of the epiglottis covers the rima glottidis, while the epiglottis itself is depressed over the larynx. The thyroid cartilage is now, by the action of the laryngeal muscles, suddenly raised up behind the hyoid bone, and thus assists the epiglottis to cover the glottis. This movement of the thyroid can easily be felt on the outside. Thus, both the entrance into the posterior nares and that into the larynx being closed, the impulse given to the bolus by the tongue can have no other effect than to propel it beneath the sloping soft palate, over the incline formed by the root of the tongue and the epiglottis. The palato-glossi or constrictores isthmi faucium, which lie in the anterior pillars of the fauces, by contracting, close the door behind the food which has passed them.

When the bolus of food is large, it is received by the middle and lower constrictors of the pharynx, which, contracting in sequence from above downwards, thrust it into the œsophagus, along which it is driven by a similar series of successive contractions which we shall speak of immediately as peristaltic action. This comparatively slow descent of the food from the pharynx into the stomach, may be readily seen if animals with long necks such as horses and dogs be watched while swallowing. When however the morsel is not large or when the substance swallowed is liquid, the movement of the back part of the tongue may be sufficient not merely to introduce the food into the grasp of the constrictors of the pharynx, but even to propel it rapidly, to shoot it in fact, along the lax œsophagus before the muscles of that organ have time to contract. In such a mode of swallowing the middle and lower constrictors take little or no part in driving the food onward, though they and the œsophagus appear to contract from above downwards after the food has passed by them, as if to complete the act and to ensure that nothing has been left behind. Deglutition in this fashion still remains possible after these constrictors have become paralysed by section of their motor nerves.

When a second act of deglutition succeeds a first with sufficient rapidity, the nervous changes which start the pharyngeal movements of the second act appear to inhibit the œsophageal movements of the first act; and when swallowing is repeated rapidly several times in succession, the œsophagus remains quiet and lax during the whole time, until immediately after the last swallow, when a peristaltic movement closes the series.

When the stethoscope is applied over the œsophagus, at different regions, a sound is heard during deglutition; sometimes two sounds are heard. The first and most constant is coincident with the passage of the bolus, and is due to this and to the muscular sound of the contracting muscles. The later and less constant sound appears to be caused by a quantity of air-bubbles with which the bolus was entangled, lodged at the cardiac end of the œsophagus, being forced into the stomach by the sequent peristaltic contraction of the œsophagus.

It will be seen, from what has been said, that deglutition, though a continuous act, may be regarded as divided into three stages. The first stage is the thrusting of the food through the isthmus faucium; this may be either of long or short duration. The second stage is the passage through the upper part of the pharynx. Here the food traverses a region common both to the food and to respiration, and in consequence the movement is as rapid as possible. The third stage is the descent through the grasp of the constrictors. Here the food has passed the respiratory orifice, and in consequence its passage again becomes comparatively slow, except in case of fluids and small morsels, when, as we have seen, it may continue to be rapid. The passage along the œsophagus may perhaps be regarded as constituting a fourth stage; but it will be more convenient to consider the œsophageal movements by themselves.

The first stage in this complicated process is undoubtedly a voluntary act. The raising of the soft palate and the approximation of the posterior pillars may also be, at times, voluntary, since they have been seen, in a case where the pharynx was laid bare by an operation, to take place before the food had touched these parts; but the movement may take place without any exercise of the will and in the absence of consciousness. Indeed the second stage taken as a whole, though some of the earlier component movements are, as it were, on the borderland between the voluntary and involuntary kingdoms, must be regarded as a reflex act. The third and last stage, whatever be the exact form which it takes, is undoubtedly reflex; the will has no power whatever over it, and can neither originate, stop, nor modify it.

Deglutition in fact as a whole is a reflex act; it cannot take place unless some stimulus be applied to the mucous membrane of the fauces. When we voluntarily bring about swallowing movements with the mouth empty, we supply the necessary stimulus by forcing with the tongue a small quantity of saliva into the fauces, or by touching the fauces with the tongue itself.

In the reflex act of deglutition, caused in the ordinary way by the food coming in contact with the fauces, the afferent impulses originated in the fauces are carried up to the nervous centre by the glosso-pharyngeal nerve, by branches of the fifth, and by the pharyngeal branches of the superior laryngeal division of the vagus. The latter seem of special importance, since the act of swallowing, quite apart from the presence of food in the mouth, may be brought out by centripetal stimulation of the superior laryngeal nerve. The efferent impulses descend the hypoglossal to the muscles of the tongue, and pass down the glosso-pharyngeal, the vagus through the pharyngeal plexus, the fifth, and the spinal accessory, to the muscles of the fauces and pharynx: their exact paths being as yet not fully known, and probably varying in different animals. The laryngeal muscles are governed by the laryngeal branches of the vagus.

The centre of the reflex act lies in the medulla oblongata. Deglutition can be excited, by tickling the fauces, in an animal rendered unconscious by removal of the brain, provided the medulla be left. If the medulla be destroyed, deglutition is impossible. The centre for deglutition lies higher up than that of respiration, so that in diseases or injuries involving the upper part of the medulla oblongata the former act may be impaired or rendered impossible while the latter remains untouched. It has been said to form part of the superior olivary bodies, but this view is based on anatomical grounds only. We shall have to deal with this and similar matters in treating of the central nervous system. It is probable that, as is the case in so many other reflex acts, the whole movement can be called forth by stimuli affecting the centre directly, and not acting on the usual afferent nerves.

§ **269**. *Peristaltic movements.* Putting aside the somewhat complicated pharyngeal part of deglutition, and taking the œsophageal movements by themselves we find that these, together with the movements of the stomach, and of the small and large intestines right down to the anus are more or less alike, and may be described under the general name of 'peristaltic' movements. We have already in § 92, spoken of these, but it may be well to consider them briefly again under a general aspect, before dwelling on the special movements of the several parts of the alimentary canal.

The muscular coat of the alimentary canal consists as we have seen of two layers, separated more or less distinctly by a sheet of connective tissue, an outer thinner longitudinal layer, and an inner thicker circular layer; and a similar arrangement obtains in nearly all the muscular hollow tubes of the body, except the arteries, in which the muscular elements are present not so much for the purpose of driving the blood onward as for the sake of regulating the irrigation.

The action of the circular coat is fairly simple. A contraction starting at any part travels onwards in the same direction, generally downwards, that is to say from a part nearer the mouth to a part nearer the rectum, for a greater or less distance, the circularly disposed bundles contracting in sequence. The result is a narrowing or constriction of the tube which, travelling more or less slowly along the tube, drives the contents onwards; when a butcher empties the intestine of a slaughtered animal by squeezing it high up with his hand or with his thumb and finger, and carrying the squeezing action downwards along the length of the intestine, he makes the passive intestine do very much what the circular coat does actively, by contraction, in the living animal.

The action of the longitudinal coat is perhaps not so clear; but a contraction of the longitudinal coat taking place in any segment of the tube would tend to draw the tube over the contents lying immediately above, or below, the segment, very much as a glove is drawn over a finger. And a succession of such contractions travelling along the tube would lead to a movement of the contents in the same direction. Were the circular coat absent a longitudinal coat might by itself possibly suffice to propel the contents along the tube. In the presence of the circular coat, the action of the longitudinal coat in any segment of the tube, if taking place immediately before the circular contraction would, by filling the segment with contents, render the squeezing action of the circular coat more efficient; if taking place immediately after the circular contraction, it would help in quickening the return of the tube to its normal calibre, for the contraction of the longitudinal coat tends to shorten and widen the segment, and thus would prepare it for new contents. We can hardly imagine that the two coats would contract at the same time, since they would tend to neutralize each other's action. Indeed we may probably go farther and assume that in each segment of the canal first the longitudinal coat contracts while the circular coat is relaxed, and that then the circular coat contracts while the longitudinal relaxes. When we come to deal with respiration we shall meet with a similar double antagonistic and successive action between inspiratory and expiratory muscles; we shall further see reason to think that the processes which start the expiratory act tend to check or inhibit the inspiratory act and vice versâ; and very possibly a like see-saw of stimulation and inhibition obtains in the muscles of the alimentary canal.

It must be remembered that the circular coat is always much thicker than the longitudinal coat; and we may infer that while the chief work of driving the contents onward falls on the former the latter assists the work, either in the way which we have suggested or in some other way.

In the small intestine the tube is hung loosely and much twisted so that many loops are formed; the contents moreover are largely fluid. Hence the steady onward movement, such as is seen when more solid contents pass along the straight and somewhat firmly attached œsophagus, is complicated by movements due to a loop being projected forward by the entrance of fluid from above, or being dragged down by the weight of its new contents, or, on the other hand, due to a loop being retracted by the driving onward of its contents and the emptying of itself, and the like. In this way a peculiar writhing movement of the bowel is brought about, and the phrase 'peristaltic movement' is generally used to denote this total effect of the contraction of the muscular coats; it will however be best to restrict the meaning to the progressive contraction of the circular coat assisted, in most cases, by a similar progressive contraction of the longitudinal coat.

§ 270. *Movements of the Œsophagus.* These as we have just said are fairly simple. The circular contraction begun by the constrictors of the pharynx is continued along the circular coat of the œsophagus and assisted by an accompanying contraction of the longitudinal coat, the direction being always, save in the abnormal action of vomiting, from above downwards.

It will be remembered (§ 222) that the muscular bundles of the œsophagus are composed of striated fibres in the upper part, and of plain unstriated fibre-cells in the lower part, the transition occupying a different level in different animals. Nevertheless, as far as the peristaltic movement is concerned, the two kinds of fibres behave in the same way except that the peristaltic wave if we may so call it travels more rapidly in the striated region.

These peristaltic movements of the œsophagus may, like those of the intestine, be seen after removal of the organ from the body; and indeed may continue to appear upon stimulation, for an unusual length of time. They may therefore be carried out by the muscular elements, with or without the help of the nervous elements embedded in them, apart from any action of the central nervous system. Nevertheless, in the living body, the movements of the œsophagus seem to be in a special way dependent on the central nervous system; the contractions are not started and carried out by the walls of the tube alone and so transmitted from section to section in the walls of the tube itself; but afferent impulses started in the pharynx and passing to the medulla oblongata, give rise to reflex efferent impulses which descend along nervous tracts to successive portions of the organ. If the œsophagus be cut across some way down, or if a portion of the middle region be excised, stimulation of the pharynx will produce a peristaltic contraction, which travelling downwards will not stop at the cut or excision but will be continued on into the lower disconnected portion by means of the central nervous system. And it is stated that ordinary peristaltic contractions of the lower part of the œsophagus can be readily excited by stimulation of the pharynx, but not by stimuli applied to its own mucous membrane. In the reflex act which thus brings about the peristaltic contraction of the œsophagus the afferent nerves are those of the pharynx, viz. the superior laryngeal nerve and pharyngeal branches of the vagus, branches of the fifth, and in some animals at least branches of the glossopharyngeal, but chiefly the first; and œsophageal movements can easily be excited by centripetal stimulation of the superior laryngeal. The centre lies in the medulla oblongata, being a part of the general deglutition centre; and the efferent impulses pass along fibres of the vagus, reaching the upper part of the œsophagus by the recurrent laryngeal nerves and the lower part through the œsophageal plexuses of the vagus (Fig. 70). Section of the trunk of the vagus renders difficult the passage of food along the œsophagus, and stimulation of the peripheral stump causes œsophageal contractions.

The force of this movement in the œsophagus is considerable; thus in the dog a ball pulling by means of a pulley against a weight of 250 grammes has been found to be readily carried down from the pharynx to the stomach.

At the junction of the œsophagus with the stomach the circular fibres usually remain in a more or less permanent condition of tonic or obscurely rhythmic contraction, more particularly when the stomach is full of food, and thus serve as a sphincter to prevent the return of food from the stomach into the œsophagus. Upon the arrival of the bolus of food at the end of the œsophagus, the centre for this sphincter is inhibited and the orifice is thus opened up. Possibly the patency of the orifice is still further secured by a contraction of the longitudinal muscular fibres which radiate from the end of the œsophagus over the stomach.

§ 271. *Movements of the Stomach.* While the object of the œsophageal movement is simply to carry the swallowed bolus with all due speed to the stomach, and while the intestinal movement has, in like manner, simply to carry the intestinal contents onward, the twisted course of the looped path ensuring all the mixing of the constituents of the contents that may be necessary, the movements of the stomach have a double object: on the one hand to provide an adequate exposure of the contents of the dilated chamber to the influence of the gastric juice, and on the other to propel the partially digested food, when ready, into the duodenum. We may accordingly distinguish between what we may call the "churning" and the "propulsive" movements of the stomach.

When the stomach is empty all the muscular fibres as we have said, longitudinal, circular and oblique, fall into a condition which we may perhaps speak of as an obscure tonic contraction. The whole stomach is small and contracted, its cavity is nearly obliterated, and the mucous membrane, owing to the predominance of the circular coat, is like the lining membrane of an empty artery, thrown into longitudinal folds. As more and more food enters the stomach all the coats become relaxed, with the exception of the pyloric sphincter, which remains at first permanently closed, and the less marked cardiac sphincter, which merely relaxes from time to time at each act of swallowing. No sooner however do the coats thus become relaxed than they set up obscure rhythmical peristaltic contractions, giving rise to the "churning" movements. These movements have been described as of such a kind that the contents flow in a main current from the cardia along the greater curvature to the pylorus, and back to the cardia along the lesser curvature, subsidiary currents mixing the peripheral portions of the contents with the more central; it may be doubted however whether any such regularity of flow is marked or constant, and it is not easy to see by what combination and sequence of contractions in the three coats, longitudinal, circular and oblique, such a regular flow can be produced. But in any case, by such rhythmical contractions the food and gastric juice are rolled about and mixed together. These churning movements are feeble at first, even though the stomach be filled and distended by a large meal rapidly eaten; they become more and more pronounced as digestion proceeds.

Before digestion has proceeded very far the 'propulsive' movements begin. These occur at intervals, and are repeated at first slowly but afterwards more rapidly. Each movement consists in a contraction of the circular muscular fibres more powerful than any taking part in the churning movements, and leading to a circular constriction which, beginning apparently at about the obscurely defined groove which marks the beginning of the antrum pylori, travels down towards the pylorus, propelling the food onward. This movement is accompanied or rather preceded by a relaxation of, that is to say in all probability an inhibition of the permanent contraction of, the sphincter pylori itself, in order that the gastric contents may pass into the duodenum. But the occurrence of this relaxation is determined by the nature of the gastric contents; for if the propulsive movement drives large undigested pieces towards the pylorus, the sphincter is apt to close again, the result of which is that the undigested morsels are carried back into the main body of the stomach.

The combined effect then of the churning and of the propulsive movements is, after a certain part of the meal has been reduced to a thick fluid condition somewhat resembling pea soup and often called chyme, to strain off this more fluid part into the duodenum, and to submit the remaining still solid pieces to the further action of the gastric juice.

As digestion proceeds, more and more material leaves the stomach, which is thus gradually emptied, the last portions which are carried through being those parts of the food which are least digestible, and any wholly indigestible foreign bodies which happen to have been swallowed; the latter may perhaps never leave the stomach at all. The presence of food leads to the development of the movements; but evidently it is not the mere mechanical repletion of the organ which is the cause of the movements, since the stomach is fullest at the beginning when the movements are slight, and becomes emptier as they grow more forcible. The one thing which does increase *pari passu* with the movements is the acidity, which is at a minimum when the (generally alkaline) food has been swallowed, and increases steadily onwards. It has not however been definitely shewn that the increasing acidity is the efficient stimulus, giving rise to the movements.

The movements of even a full stomach are said to cease during sleep. The nervous mechanism of the gastric movements had better be considered in connection with that of the intestinal movements.

§ **272** *Vomiting.* In a conscious individual this act is preceded by feelings of nausea, during which a copious flow of saliva into the mouth takes place. This being swallowed carries down with it a certain quantity of air, the presence of which in the stomach, by assisting in the opening of the cardiac sphincter, subsequently facilitates the discharge of the gastric contents. The nausea is generally succeeded at first by ineffectual retching in which a deep inspiratory effort is made, so that the diaphragm is thrust down as low as possible against the stomach, the lower ribs being at the same time forcibly drawn in; since during this inspiratory effort the glottis is kept closed, no air can enter into the lungs; but some is drawn into the pharynx, and thence probably descends by a swallowing action into the stomach. When retching passes on to actual vomiting this inspiratory effort is succeeded by a sudden violent expiratory contraction of the abdominal walls, the glottis still being closed, so that the whole force of the effort is spent, as we shall see it is in defæcation, in pressure on the abdominal contents. The stomach is therefore forcibly compressed from without. At the same time, or rather immediately before the expiratory effort, by a contraction of its longitudinal fibres the œsophagus is shortened and the cardiac orifice of the stomach brought close under the diaphragm, while apparently by an inhibition of the circular sphincter, aided perhaps by a contraction of the fibres which radiate from the end of the œsophagus over the stomach, the cardiac orifice, which is normally closed, is somewhat suddenly dilated. This dilation opens a way for the contents of the stomach, which, pressed upon by the contraction of the abdomen, and to a certain but probably only to a slight extent by the contraction of the gastric walls, are driven forcibly up the œsophagus. The mouth being widely open, and the neck stretched to afford as straight a course as possible, the vomit is ejected from the body. At this moment there is an additional expiratory effort which serves to prevent the vomit passing into the larynx. In most cases too the posterior pillars of the fauces are approximated, in order to close the nasal passage against the ascending stream. This however in severe vomiting is frequently ineffectual.

Thus in vomiting there are two distinct acts; the dilation of the cardiac orifice and the extrinsic pressure of the abdominal walls in an expiratory effort. Without the former the latter, even when distressingly vigorous, is ineffectual. Without the latter, as in urari poisoning, the intrinsic movements of the stomach itself are rarely sufficient to do more than eject gas, and, it may be, a very small quantity of food or fluid. Pyrosis or waterbrash is however probably brought about by this intrinsic action of the stomach.

During vomiting the pylorus is generally closed, so that but little material escapes into the duodenum. When the gall-bladder is full, a copious flow of bile into the duodenum accompanies the act of vomiting. Part of this may find its way into the stomach, as in bilious vomiting, the pylorus then having evidently been opened.

The nervous mechanism of vomiting is complicated and in many aspects obscure. The efferent impulses which cause the expiratory effort must come from the respiratory centre in the medulla; with these we shall deal in speaking of respiration. The dilation of the cardiac orifice is caused, in part at least, by impulses descending the vagi, since when these are cut real vomiting with discharge of the gastric contents, if it takes place at all, becomes difficult through want of readiness in the dilation. Such intrinsic movements of the stomach as do take place, and the movements of the œsophagus appear to be carried out by the usual nerves. The efferent impulses which cause the flow of saliva in the introductory nausea also descend along the usual nerves such as the chorda tympani. These various impulses may best be considered as starting from a vomiting centre in the medulla, having close relations with the respiratory centre. This centre may be excited, may be thrown into action, in a reflex manner, by stimuli applied to peripheral nerves, as when vomiting is induced by tickling the fauces, or by irritation of the gastric membrane, or by obstruction of the intestine due to ligature, hernia, etc. That the vomiting in the last instance is due to nervous action, and not to any regurgitation of the intestinal contents, is shewn by the fact that it will take place when the intestine is perfectly empty and may be prevented by section of the mesenteric nerves. The vomiting attending renal and biliary calculi is apparently also reflex in origin. Vomiting in fact as a rule is a reflex action, the afferent impulses passing along one or other nerves, but most frequently along those connected with the alimentary canal, that is along afferent fibres running in the vagus or in the splanchnic nerves. The centre however may be affected directly, as probably in the cases of some poisons, and in some instances of vomiting from disease of the medulla oblongata. Lastly, it may be thrown into action by impulses reaching it from parts of the brain higher up than itself, as in cases of vomiting produced by smells, tastes or emotions, or by the recollection of past events, and in some cases of vomiting due to cerebral disease.

Many emetics, such as tartar emetic, appear to act directly on the centre, since, introduced into the blood, they will produce vomiting after a bladder has been substituted for the whole stomach. Others again, such as mustard and water, act in a reflex manner by irritation of the gastric mucous membrane. With others, again, which cause vomiting by developing a nauseous taste, the action involves parts of the brain higher than the centre itself.

§ **273**. *Movements of the Small Intestine.* These, as we have already said, are the typical peristaltic movements, simple except in so far as they are complicated by the existence of the pendent loops, the peculiar oscillating movements of which appear to be produced chiefly by the longitudinal fibres.

The peristaltic movements, as a rule, take place from above downwards, and a wave beginning at the pylorus may be traced a long way down. But contractions may, and in all probability occasionally do, begin at various points along the length of the intestine. A movement started by artificial stimulation some way down the intestine, may travel not only downwards but also upwards; it has been disputed however, whether in the living body any natural backward peristaltic movement really takes place. In the living body the intestines have periods of rest, alternating with periods of activity, the occurrence of the periods depending on various circumstances; the intensity of the movements also varies very considerably.

§ **274**. *Movements of the Large Intestine.* These are fundamentally the same as those of the small intestine, but distinct in so far as the latter cease at the ileo-cæcal valve, at which spot the former normally begin; they are simpler, in as much as the pendent loops are absent, and not so vigorous, since relatively to the diameter of the tube, the amount of muscular fibre is less. Along the colon where the sacculi are well developed (§ 266) the movement may perhaps be described as almost intermittent from sacculus to sacculus, the contents of one sacculus being driven by the peristaltic contractions of its circular fibres into the next sacculus, which prepares to receive them by a relaxation of its circular and a contraction of its longitudinal fibres.

Since the lips of the ileo-cæcal valve are placed transversely across the cæcum, not only does distension of the cæcum, by stretching the valve along the line of the lips, bring them into apposition, but the pressure exerted by the peristaltic movement has the same effect. In this way any return of the contents from the large to the small intestine is prevented.

Arrived at the sigmoid flexure, the contents, now more or less solid fæces, are supported by the bladder and the sacrum, so that they do not press on the sphincter ani.

§ **275**. *Defæcation.* This is a mixed act, being superficially the result of an effort of the will, and yet carried out by means of an involuntary mechanism. Part of the voluntary effort consists in producing a pressure-effect, by means of the abdominal muscles. These are contracted forcibly as in expiration, but the glottis being closed and the escape of air from the lungs prevented, the whole force of the pressure is brought to bear on the abdomen itself, and so drives the contents of the descending colon onward towards the rectum. The sigmoid flexure is by its position sheltered from this pressure; a body introduced per anum into the empty rectum is not affected by even forcible contractions of the abdominal walls.

The anus is guarded by the sphincter ani, which is habitually in a state of normal tonic contraction, capable of being increased or diminished by a stimulus applied, either internally or externally, to the anus. The tonic contraction is in part at least due to the action of a nervous centre situated in the lumbar spinal cord. If the nervous connection of the sphincter with the spinal cord be broken, relaxation takes place. If the spinal cord be divided somewhat higher up, for instance in the dorsal region, the sphincter, after the depressing effect of the operation, which may last several days, has passed off, regains and subsequently maintains its tonicity, shewing that the centre is not placed higher up than the lumbar region of the cord. The increased or diminished contraction following on local stimulation is probably due to reflex augmentation or inhibition of the action of this centre. The centre is also subject to influences proceeding from higher regions of the cord, and from the brain. By the action of the will, by emotions, or by other nervous events, the lumbar sphincter centre may be inhibited, and thus the sphincter itself relaxed; or augmented, and thus the sphincter tightened. A second item therefore of the voluntary process in defæcation is the inhibition of the lumbar sphincter centre, and consequent relaxation of the sphincter muscle. Since the lumbar centre may remain wholly efficient when separated from the brain, the paralysis of the sphincter which occurs in certain cerebral diseases is probably due to inhibition of this lumbar centre, and not to paralysis of any cerebral centre.

Thus a voluntary contraction of the abdominal walls, accompanied by a relaxation of the sphincter, might press the contents of the descending colon into the rectum and out at the anus. Since however, as we have seen, the pressure of the abdominal walls is warded off the sigmoid flexure, such a mode of defæcation would always end in leaving the sigmoid flexure full. Hence the necessity for these more or less voluntary acts being accompanied by an involuntary augmentation of the peristaltic action of the large intestine, sigmoid flexure and rectum.

In the movements of the rectum we can trace out more distinctly than in other regions of the alimentary canal the separate actions of the longitudinal and circular fibres. The former, by means of contractions travelling from above downwards, shorten the rectum, and since the anus affords a more or less fixed support pull the rectum and its contents down; the latter, by means of contractions travelling from above downwards but taking place somewhat later, narrow the rectum and so squeeze the contents onwards and outwards.

Defæcation then appears to take place in the following manner. The large intestine and sigmoid flexure becoming more and more full, stronger and stronger peristaltic action is excited in their walls. By this means the fæces are driven into the rectum and so, by a continuance of the movements increasing in vigour, against the sphincter. Through a voluntary act, or sometimes at least by a simple reflex action, the lumbar sphincter centre is inhibited and the sphincter relaxed. At the same time the contraction of the abdominal muscles presses firmly on the descending colon, and thus, contractions of the levator ani assisting, the contents of the rectum are ejected.

It must however be remembered that, while in appealing to our own consciousness, the contraction of the abdominal walls and the relaxation of the sphincter seem purely voluntary efforts, the whole act of defæcation, including both of these seemingly so voluntary components, may take place in the absence of consciousness, and indeed, in the case of the dog at least, after the complete severance of the lumbar from the dorsal cord. In such cases the whole act must be purely reflex, excited by the presence of fæces in the rectum.

§ **276**. *The nervous mechanisms of gastric and intestinal movements.* Both the stomach and intestines when removed from the body and thus wholly separated from the central nervous system may, by direct stimulation, be readily excited to movements; and indeed in the absence of all obvious stimuli, movements which seem to be spontaneous may at times be observed. The movements of which we are speaking are orderly movements of a peristaltic nature, not mere local contractions of a few bundles of plain muscular fibres. The alimentary canal therefore, like the heart, though to a less degree, possesses within itself such mechanisms as are requisite for carrying out its own movements; and, as in the case of the heart, there is no adequate evidence that the ganglia scattered in its muscular walls, those namely forming the plexus of Auerbach, play any prime part in developing these movements.

On the other hand, powerful movements of a peristaltic kind may be induced, not only as we have already seen in the œsophagus but also in the stomach, in the small intestine, and even in the large intestine by stimulation of the vagus nerve.

The chief and usual cause of the movements of the stomach and intestines is the presence of food in their interior. But we do not know definitely the exact manner in which the food produces the movement. It may be that the food, by stimulating the mucous membrane, sends up afferent impulses, and that these give rise by reflex action to efferent impulses which descend the vagus fibres to successive portions of the canal, in a manner similar to that already described in reference to the œsophagus. If this be so the efferent impulses reach the stomach and upper part of the duodenum by the terminal portions of the two vagi, Fig. 70, *R.V. L.V.*, and reach the intestines by the portion of the right or posterior vagus, Fig. 70, *R′.V′.*, which passes into the solar plexus and thence by the mesenteric nerves. The afferent impulses from the stomach travel also apparently by the vagus; the paths of those from the intestines have not yet been determined.

But that such a reflex action through vagus fibres is not the only means by which the presence of food brings about the movements in question, is shewn by the fact that these continue to be developed after section of both vagus nerves. Probably the whole action is a mixed one which we may picture to ourselves somewhat as follows. The alimentary canal possesses a power of spontaneous movement, feeble it is true, very inferior to that of the heart, and very apt to be latent, but still existing. The presence of food in some way or other, by some direct action quite apart from the central nervous system, is able to increase this power so that, without any aid from the central nervous system, as after section of the vagi, adequate peristaltic movements can, under favourable circumstances, be carried out. Nevertheless in the normal course of events satisfactory movements are still further secured by the reflex action through vagus fibres just described. Thus, in the dog, the act of swallowing food or even the mere smell of food has been observed to increase the movements of a piece of intestine isolated from the rest of the alimentary canal but retaining its connections with the central nervous system. Under this view the peristaltic movements produced by centrifugal stimulation of the vagus in the neck are comparable not so much with the contraction of a skeletal muscle when its motor nerve is stimulated as with the beats which may be called forth in an inhibited or otherwise quiescent heart by stimulation of the cardiac augmentor fibres.

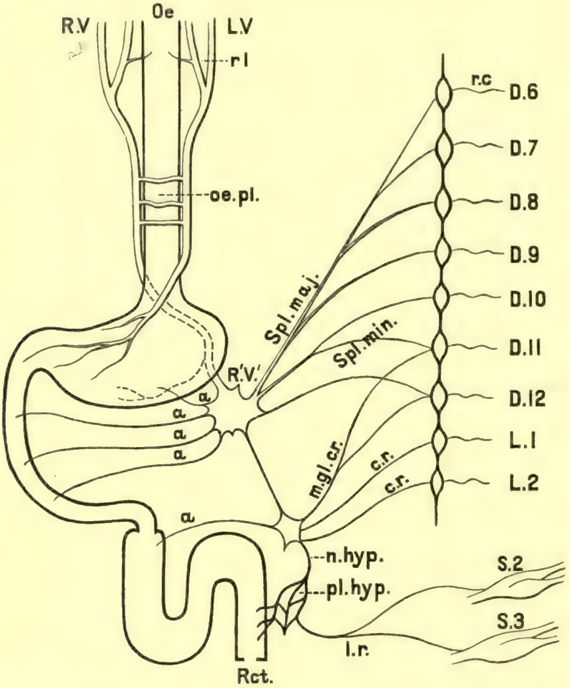

Fig. 70. Diagram to illustrate the Nerves of the Alimentary Canal in the Dog.

The figure is for the sake of simplicity made as diagrammatic as possible, *and does not represent the anatomical relations.*

Oe to *Rct.*—The alimentary canal, œsophagus, stomach, small intestine, large intestine, rectum.

LV. Left vagus nerve, ending on front of stomach. *r.l.* recurrent laryngeal nerve supplying upper part of œsophagus. *R.V.* right vagus, joining left vagus in œsophageal plexus, *oe. pl.*, supplying the posterior part of stomach and continued as *R'.V'.* to join the solar plexus, *here represented by a single ganglion* and connected with the inferior mesenteric ganglion (or plexus) *m. gl.*—*a.* branches from the solar plexus to stomach and small intestine, and from the mesenteric ganglion to the large intestine.

Spl. maj. Large splanchnic nerve arising from the thoracic ganglia and rami communicantes *r.c.* belonging to dorsal nerves from the 6th to the 9th (or 10th).

Spl. min. Small splanchnic nerve similarly arising from 10th and 11th dorsal nerves. These both join the solar plexus and thence make their way to the alimentary canal.

C.r. Nerves from the ganglia &c. belonging to 11th and 12th dorsal and 1st and 2nd lumbar nerves, proceeding to the inferior mesenteric ganglia (or plexus) *m. gl.* and thence by the hypogastric nerve *n. hyp.* and the hypogastric plexus *pl. hyp.* to the circular muscles of the rectum.

l.r. Nerves from the 2nd and 3rd sacral nerves, *S*2, *S*3 (nervi erigentes), proceeding by the hypogastric plexus to the longitudinal muscles of the rectum.

Indeed we may perhaps call the vagus fibres which pass to the stomach and intestines (and these we may remark are, like the cardiac augmentor fibres, non-medullated fibres along the greater part of their course) augmentor fibres rather than motor fibres. We have all the more reason to do so since there exist companion but antagonistic inhibitory fibres. If while lively peristaltic action is going on in the bowels, the splanchnic nerves be stimulated the bowels are brought to rest, often in a very abrupt and marked manner. Inhibitory fibres therefore run in the splanchnic nerves, Fig. 70, *Spl. maj.* and *min.*, passing along them from the spinal cord to the abdominal plexuses, and thence to the alimentary canal; probably some of the fine medullated fibres which may be observed along this track are of this nature.

It will be noticed that the splanchnic nerves while containing vaso-constrictor *i.e.* augmentor fibres for the blood vessels of the intestines, carry inhibitory fibres for the muscular coat; and probably the vagus while containing augmentor fibres for the muscular coat carries inhibitory dilator fibres for the blood vessels. It may further be remarked that the vagus while supplying augmentor fibres for the muscular mechanisms of the alimentary canal carries, as we so well know, inhibitory fibres for the cardiac muscular mechanism.

In the above statement we have purposely used the general term peristaltic movement, but as we have seen, in the movements of the alimentary canal, two sets of muscles are concerned, the circular and the longitudinal. Now in the rectum we are able to recognise that the two sets of muscles have quite distinct nervous supplies. The longitudinal coat is governed by nerve-fibres which, in the dog, leave the spinal cord in the anterior roots of the second and third sacral nerves, Fig. 70, *S*2, *S*3, pass along the branches of those nerves, frequently spoken of as the *nervi erigentes*, *l. r.*, to the hypogastric plexus, *pl. hyp.*, and thence to the rectum. Stimulation of these nerves causes contractions of the rectum which are confined to the longitudinal coat and as we have said pull the rectum down. The circular coat is governed by fibres which leave the spinal cord by the anterior roots of the lower dorsal and first two lumbar nerves, Fig. 70 (coming from the lower part of that spinal region from which as we have seen § 169 the vaso-constrictor fibres take origin), and, early losing their medulla, pass to the rectum by the inferior mesenteric ganglia, the hypogastric nerves and hypogastric plexus, Fig. 70, *m. gl.*, *n. hyp. pl.*, *hyp.* Stimulation of these fibres gives rise to contractions which are confined to the circular coat, and squeeze out the contents of the rectum. A similar double nervous supply probably governs the longitudinal and circular coats along the whole alimentary canal; but the details of such a supply are at present unknown.

Our knowledge moreover concerning the details of any special nervous mechanisms, by means of which the more complicated movements of the stomach, including the closing and opening of the sphincters, are carried out, is at present very imperfect. We cannot add to what we have incidentally said in speaking of vomiting.

The movements of the rectum, including the sigmoid flexure, appear to be much more closely dependent on the central nervous system than are those of the rest of the alimentary canal. As we have said the movements of both large and small intestine are rather assisted and augmented than primarily called forth by impulses descending from the central nervous system along the vagus fibres. As the large intestine however passes into the rectum government by the vagus is replaced by government through the lumbar cord and the nerves just previously mentioned; and this government appears to be not so much mere augmentation as the actual carrying out of the movements through reflex action. Hence this is the part of intestinal movement which fails in diseases of the central nervous system; the failure leading to obstinate constipation if not to actual difficulty of defæcation. The presence of fæces in the sigmoid flexure no longer stirs up the reflex mechanism for their discharge; meanwhile the more independent movements of the higher parts of the canal continue to drive the contents onward; and hence the fæces accumulate in the sigmoid flexure and colon awaiting the delayed action of the imperfect reflex mechanism. With regard to the exact manner in which the presence of food acts as a stimulus it may be worth while to remark, that, though in the stomach as we have seen mere fulness is not the efficient cause of the movements, since these become more active as digestion proceeds and the bulk of the contents diminishes, yet in the intestine distension of the bowel up to certain limits most distinctly increases the vigour of the movements just as distension of the cardiac cavities within certain limits improves the cardiac stroke. This is well seen in obstruction of the bowels in which cases the bowel distended above the obstruction is frequently thrown into violent peristaltic movements. This effect is in part at least due to the distension extending the muscular fibres and so in a direct manner promoting their contraction (see § 81), but may be in part due to augmentor impulses excited in a reflex manner. Probably in an intestine isolated from the central nervous system, food provokes peristaltic movements much more by causing distension and so stretching the muscular coats than by acting as a stimulus to the mucous membrane either through chemical action or in any similar way.

§ **277.** Next to the presence of food in the interior of the alimentary canal, a deficient oxygenation of the blood supplied to the walls of the canal or the sudden cutting off of the supply of blood, may be regarded as the most powerful provocatives of peristaltic action. When the aorta is clamped or when the respiration is seriously interfered with, peristaltic movements become very pronounced. Thus, in death by asphyxia or suffocation, an involuntary discharge of fæces, which is in part at least the result of increased peristaltic action, is not an unfrequent result; and the marked peristaltic movements which are so frequently seen in an animal when the abdomen is laid open immediately after death, appear to be due to the cessation of the circulation and the consequent failure in the supply of blood to the walls of the alimentary canal and not, as has been suggested, to the contact with air of the peritoneal surface. Since it is blood which brings oxygen to the tissues, failure in the supply of blood is tantamount to failure in the supply of oxygen; but the blood current brings other things besides oxygen and also takes things away; and the failure of this action also probably, as well as failure in the supply of oxygen, provokes the movements in question.

The movements thus produced are to some extent the result of the deficient supply of blood acting directly on the walls of the canal, though in asphyxia at all events this effect may be increased by the too venous blood stimulating the central nervous system and thus sending augmentor impulses down the vagus.

With regard to the mode of action of the drugs which promote peristaltic action it will be sufficient here to say that while some such as nicotin appear to act directly on the walls of the canal, others such as strychnia produce their effect chiefly by acting through the central nervous system.

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SEC. 8. THE CHANGES WHICH THE FOOD UNDERGOES IN THE ALIMENTARY CANAL.

§ 278. Having studied the properties of the digestive juices as exhibited outside the body, and the various mechanisms by means of which the food introduced into the body is brought under the influence of those juices, we have now to consider what, as matters of fact, are the actual changes which the food does undergo in passing along the alimentary canal, what are the steps by which the contents of the canal are gradually converted into fæces. The events which lead to this conversion are two-fold. On the one hand the digestive juices do bring about, inside the alimentary canal, changes which in the main are the same as those observed in laboratory experiments outside the body and described in previous sections, though the results are somewhat modified by the special conditions which obtain within the body. On the other hand absorption, that is to say, the passage from the interior of the canal into the blood vessels and lymphatics, of digested material in company with water, is going on along the whole length of the canal, and especially in the small and large intestines. It will be convenient to confine ourselves at present to the study of the first class of events, the changes effected in the canal, merely noting the disappearance of this or that product, and deferring the difficult problem of how absorption takes place to a subsequent and separate discussion.

In the mouth the presence of the food, assisted by the movements of the jaw, causes, as we have seen, a flow of saliva. By mastication, and by the addition of mucous saliva, the food is broken into small pieces, moistened, and gathered into a convenient bolus for deglutition. In man some of the starch is, even during the short stay of the food in the mouth, converted into sugar; for if boiled starch free from sugar be even momentarily held in the mouth, and then ejected into water (kept boiling to destroy the ferment) it will be found to contain a decided amount of sugar. In many animals no such change takes place. The viscid saliva of the dog serves almost solely to assist in deglutition; and even the longer stay which food makes in the mouth of the horse is insufficient to produce any marked conversion of the starch it may contain. During the rapid transit through the *œsophagus* no appreciable change takes place.

The amount of absorption of digested material, or even of simple water from the mouth or œsophagus, must always be insignificant.

The Changes in the Stomach.

§ 279. The arrival of the food, the reaction of which is either naturally alkaline, or is made alkaline, or at least is reduced in acidity, by the addition of saliva, causes a flow of gastric juice. This, already commencing while the food is as yet in the mouth, increases as the food accumulates in the stomach, and as, by the churning gastric movements, one part after another of the food is brought into contact with the mucous membrane.

The characters of the juice appear to change somewhat as the act of digestion proceeds. The amount of pepsin in the gastric contents increases for some time after food is taken, and probably the actual secretion increases also. The acidity of the gastric contents is at first very feeble; indeed in man, in some cases at least, for some little time after the beginning of a meal no free acid is present, and during this period the conversion of starch into sugar may continue. This condition however is temporary only; very soon the contents become acid, arresting the action of and ultimately destroying the amylolytic ferment; and, since the rate of the secretion of acid appears to be fairly constant, the contents of the stomach, unless fresh alkaline food be taken, become more acid as digestion goes on.

The gross effect of gastric digestion is to break up and partly to dissolve the larger lumps of masticated food into a thick greyish soup-like liquid called *chyme*, with which are still mixed in variable quantity larger and smaller masses of less changed food. This is the result, partly of the solution of proteid matters, partly of the solution of the gelatiniferous connective-tissue holding the proteid elements together. In a fragment of meat, for instance, the muscular fibres, through the solution of the connective-tissue binding them together, fall asunder, the sarcolemma is dissolved, and the fibres themselves split up sometimes longitudinally but most frequently by transverse cleavage into discs, and are ultimately more or less reduced partly into a granular mass, partly to actual solution. In a piece of tissue containing fat, the connective-tissue binding the fat cells together and the envelopes of the fat cells are dissolved, so that the fat, fluid at the temperature of the body, is set free from the individual cells and runs together into larger and smaller masses. In vegetable tissue the proteid elements are in part dissolved and, though there is no evidence that in man cellulose is dissolved in the stomach, the whole tissue is softened and to a certain extent disintegrated. Milk is curdled and the curd subsequently more or less dissolved.

The thick soup-like acid chyme consists accordingly partly of substances which have entered into actual solution, partly of mere particles or droplets of proteid, fatty or other nature and partly of masses small or great, which may be recognized under the microscope as more or less changed portions of animal or vegetable tissue. The amount of material actually dissolved is in most specimens of chyme exceedingly small. When the solid parts are removed by filtration the clear filtrate contains besides salts, pepsin and free hydrochloric acid (the constituents of the gastric juice), a small amount of sugar, of parapeptone and of peptone. The sugar is often absent, the parapeptone is not always present, and the amount of peptone (or albumose) is always small.

During gastric digestion the chyme thus formed is from time to time ejected through the pylorus, accompanied by even large morsels of solid less-digested matter. This may occur within a few minutes of food having been taken; but the larger escape from the stomach probably does not in man begin till from one to two, and lasts from four to five hours, after the meal, becoming more rapid towards the end, and such pieces as are the least broken up by the gastric juice and movements being the last to leave the stomach.

The time taken up in gastric digestion probably varies in the same animal not only with different articles of food but also with varying conditions of the stomach and of the body at large. In different animals it varies very considerably, being from 12 to 24 hours in the dog after a full meal, while the stomachs of rabbits are never empty but always remain largely filled with food, even during starvation. In man the stomach probably becomes empty between the usual meals.

The total amount of change which the food undergoes in the stomach, that is the share taken by the stomach in the whole work of digestion, seems to vary largely in different animals, and in the same animal differs according to the nature of the meal. In a dog fed on an exclusively meat diet, a very large part of the digestion is said to be carried out by the stomach, very little work apparently being left for the intestines; that is to say, the larger part of the meal is reduced in the stomach to actual solution and a considerable quantity is probably absorbed directly from the stomach. In such cases the amount of peptone found in the stomach during the digestion of the meal is found to be fairly constant, from which it may be inferred that the peptone is absorbed as soon as it is formed. There is also evidence that fat may to a certain extent undergo in the stomach changes leading to emulsion, similar to those which, as we shall see, are carried out in the small intestine.

But such cases as these cannot be regarded as typical cases of gastric digestion, and in man, at all events, living on a mixed diet the work of the stomach appears to be to a large extent preparatory only to the subsequent labours of the intestine. It is true that our information on this matter is imperfect, being chiefly drawn from the study of cases of gastric or duodenal fistula, in which probably the order of things is not normal, or being in large measure deductions from experiments on animals, whose economy in this respect must be largely different from our own; but we are probably safe in concluding that, in ourselves, the chief effect of gastric digestion is by means of the disintegration spoken of above to reduce the lumps of food to the more uniform chyme and so to facilitate the changes which take place in the small intestine. During that disintegration some of the proteid in the meal is converted into peptone; and the peptone so formed is probably absorbed at once; but much proteid remains unchanged or at least is not converted into peptone, and the fats and starches undergo in themselves very little change indeed.

In the act of swallowing, no inconsiderable quantity of air is carried down into the stomach, entangled in the saliva, or in the food. This is returned in eructations. When the gas of eructation or that obtained directly from the stomach is examined, it is found to consist chiefly of nitrogen and carbonic acid, the oxygen of the atmospheric air having been largely absorbed. In most cases the carbonic acid is derived by simple diffusion from the blood, or from the tissues of the stomach, which similarly take up the oxygen. In many cases of flatulency, however, it may arise from a fermentative decomposition of the sugar which has been taken as such in food or which has been produced from the starch, the gas being either formed in the stomach or passing upwards from the intestine through the pylorus.

The enormous quantity of gas which is discharged through the mouth in cases of hysterical flatulency, even on a perfectly empty stomach, and which seems to consist largely of carbonic acid, presents difficulties in the way of explanation; it is possible that it may be simply diffused from the blood, but it is also possible that in many cases it is derived from air which the patient has hysterically swallowed, the oxygen having been removed, in the stomach, by absorption and replaced by carbonic acid.

In the Small Intestine.

§ **280.** The semi-digested acid food, or chyme, as it passes over the biliary orifice, causes as we have seen (§ 253) gushes of bile, and at the same time the pancreatic juice flows into the intestine freely. These two alkaline fluids, especially the more strongly and constantly alkaline pancreatic juice, tend to neutralize the acidity of the chyme, but the contents of the duodenum do not become distinctly alkaline until some distance from the pylorus is reached. The rapidity with which the change in the reaction is completed is not the same in all animals, and in the same animal appears to vary according to the nature of the food, and various circumstances. In man, living on a mixed diet, the contents have probably become distinctly alkaline before they have passed far down the duodenum. On the other hand in dogs, the contents of the small intestine have been observed to be acid throughout, and that, not only when fed on starch and fat, which might, by an acid fermentation of which we shall presently speak, give rise to an acid reaction, but even when fed on meat.

The conversion of starch into sugar, which as we have seen is sooner or later arrested in the stomach, is resumed with great activity and indeed completed by the pancreatic juice, possibly assisted by the succus entericus, the presence of bile being said to increase the activity of the pancreatic amylolytic ferment. The conversion begins as soon as the acidity of the chyme is sufficiently reduced and continues along the intestine; portions however of still undigested starch may be found in the large intestine, and even at times in the fæces.

The pancreatic juice, as we have seen, emulsifies fats, and also splits them into their respective fatty acids and glycerine. The fatty acids thus set free become converted by means of the alkaline contents of the intestine into soaps; but to what extent saponification thus takes place is not exactly known. Undoubtedly soaps have to a small extent been found both in portal blood and in the thoracic duct after a meal; but there is no proof that any large quantity of fat is introduced in this form into the circulation. On the other hand, the presence of neutral fats in the lacteals, and to a slight extent in portal blood, is a conspicuous result of the digestion of fatty matters; and in all probability saponification in the intestine is a subsidiary process, the effect of which is rather to facilitate the emulsion of neutral fats than to introduce soaps as such into the blood. For the presence of soluble soaps favours the emulsion of neutral fats. Hence a rancid fat, *i.e.* a fat containing a certain amount of free fatty acid, forms an emulsion with an alkaline fluid more readily than does a quite neutral fat. A drop of rancid oil let fall on the surface of an alkaline fluid, such as a solution of sodium carbonate of suitable strength, rapidly forms a broad ring of emulsion, and that even without the least agitation. As saponification takes place at the junction of the oil and alkaline fluid currents are set up, by which globules of oil are detached from the main drop and driven out in a centrifugal direction; the intensity of the currents and the consequent amount of emulsion depend on the concentration of the alkaline medium and on the solubility of the soaps which are formed. Now the bile and pancreatic juice supply just such conditions as the above for emulsionizing fats: they both together afford an alkaline medium, the pancreatic juice gives rise to an adequate amount of free fatty acid, and the bile in addition brings into solution the soaps as they are formed. So that we may speak of the emulsion of fats in the small intestine as being carried on by the bile and pancreatic juice acting in conjunction; and as a matter of fact the bile and pancreatic juice do largely emulsify the contents of the small intestine, so that the greyish turbid chyme is changed into a creamy-looking fluid, which has been sometimes called chyle. It is advisable however to reserve this name for the contents of the lacteals. Many of the fats present in food, for instance, butter, already contain some fatty acids when eaten; for these fats the initial action of the pancreatic juice is less necessary.

This mutual help of bile and pancreatic juice in producing an emulsion explains to a certain extent the controversy which long existed between those who maintained that the bile and those who maintained that the pancreatic juice was necessary for the digestion and absorption of fatty food. That the pancreatic juice does produce in the intestine such a change as favours the transference of neutral fats from the intestine into the lacteals, is shewn by the fact that in diseases affecting the pancreas, much fatty food frequently passes through the intestine undigested, and great wasting ensues; but it cannot be maintained that the pancreatic juice is the sole agent in this matter, since in animals in which the pancreatic ducts have been successfully ligatured chyle is still found in the lacteals. On the other hand, that the bile is of use in the digestion of fat is shewn by the prevalence of fatty stools in cases of obstruction of the bile-ducts; and though the operation of ligaturing the bile-ducts, and leading all the bile externally through a fistula of the gall bladder, is open to objection, since it, in some way or other, so exhausts the animal as indirectly to affect digestion, still the results of experiments in which the resorption of fat was distinctly lessened (the quantity of fat in the lacteals falling from 3·2 to ·02 p.c.) by the ligature and fistula, obviously point to the same conclusion. That in man the succus entericus possesses a wholly insufficient emulsifying power is shewn by the observation of a case in which the duodenum opened on the surface by a fistula in such a way that the lower part of the intestine could be kept free from the contents of the upper part containing the bile and pancreatic juice and matters proceeding from the stomach. Fats introduced into the lower part, where they could not be acted upon either by the bile or by the pancreatic juice were but slightly digested. Without denying the possible assistance of the succus entericus, or even of gastric juice, we may conclude that the digestion of fat is in the main carried out by the conjoint action of bile and pancreatic juice.

§ 281. We have seen, § 247, that the addition of bile to a digesting mixture gives rise to a precipitate. This is partly a coarse flocculent precipitate, consisting of parapeptone with some amount of bile acids, and partly of a finer more granular precipitate, which is longer in falling down, and consists chiefly of bile acids with a variable amount of peptone; the latter is re-dissolved on the further addition of bile even though the reaction of the mixture remain acid. In the upper part of the duodenum the inner surface, if examined while digestion is going on, is found to be lined by a coloured flocculent and granular material, which is probably a precipitate thus formed; the purpose of this precipitation is probably to delay the passage of the undigested parapeptone along the duodenum. Moreover, apart from this precipitation, bile arrests the action of pepsin, even while the reaction of the mixture still remains acid; and as soon as an alkaline reaction is established the pepsin is apparently destroyed by the trypsin, so that with the flow of bile and pancreatic juice into the duodenum the processes which have been going on in the stomach come to an end. In fact it would seem that the juices of the various districts of the alimentary canal are mutually destructive; thus, while pepsin in an acid solution destroys the active constituents of saliva and of pancreatic juice (probably also those of the succus entericus), it is in its turn antagonized or destroyed by the bile and the other alkaline juices of the intestine. Hence pancreatic juice introduced through the mouth must lose its powers in the stomach and can only be of use as an alkaline medium containing certain proteid matters. On the other hand if, as we have reason to believe, the contents of the stomach as they issue from the pylorus still contain a large quantity of undigested proteids, these must be digested by the pancreatic juice (with or without the assistance of the succus entericus), the action of which seems to be assisted or at least not hindered by bile. And in dogs fed through a duodenal fistula, so that all gastric digestion is excluded, proteids are completely digested and give rise to quite normal fæces. To what stage the pancreatic digestion is carried, whether peptone is, practically, the only product, or whether the pancreatic juice in the body, as out of the body, carries on its work in the more destructive form, whereby the proteid material subjected to it is so broken down as to give rise to appreciable quantities of leucin and tyrosin, is at present not exactly known. Leucin and tyrosin have been found in the intestinal contents, and may therefore be formed during normal digestion, but whether an insignificant quantity or a considerable quantity of the proteid material of food is thus hurried into a crystalline form cannot be definitely stated. The extent to which the action is carried is probably different in different animals, and probably varies also according to the nature of the meal and the condition of the body. Possibly when a large and unnecessary quantity of proteid material is taken at a meal together with other substances, no inconsiderable amount of the proteids undergo this profound change, and, as we shall see, rapidly leave the body as urea, without having been used by the tissues, their contribution to the energy of the body being limited to the heat given out during the changes by which they are converted into urea. To this apparently wasteful use of proteids we shall return in speaking of what is called the 'luxus consumption' of food.

§ **282.** In dealing with the action of pancreatic juice we drew attention, § 249, to the difference between the results of pure tryptic digestion and those obtained when bacteria or other micro-organisms were allowed to be present. We saw that indol, for example, was the product of the action of these organisms, not of trypsin. Now indol is formed, in varying quantity, during the digestion which actually takes place in the intestine, some of it at times appearing in the urine as indigo-yielding substance (indican). Moreover bacteria and other micro-organisms are present in the intestinal contents. Hence we must regard the changes taking place in the intestine not as the pure results of the action of the several digestive juices, but as these results modified by or mixed with the results of the action of micro-organisms. We spoke above, § 247, of bile as being antiseptic, but this must be understood as meaning not that the presence of bile arrests the action of all micro-organisms within the intestine, but that it modifies their action, keeping it within certain limits and along certain lines.

Concerning the exact nature and extent of the changes thus due to micro-organisms our knowledge is at present very imperfect. The proteids and the carbohydrates seem to be the food stuffs on which these organisms produce their chief effect. Out of the proteids they give rise not only to indol but to several other compounds, among which may be mentioned phenol (C_6H_6O), of which a small quantity may be recognized in the fæces, the rest being absorbed and appearing in the urine in the form of certain phenol-compounds, such as phenyl-sulphuric acid. Out of proteids they may also form the peculiar poisonous bodies called *ptomaines*, which appear in the ordinary putrefaction of proteids. But their most conspicuous effects are those on the carbohydrates. As the food descends the intestine, the presence of lactic acid becomes more and more obvious; indeed in some cases the naturally alkaline reaction of the intestinal contents may in the lower part of the intestine be changed into an acid one by the presence of lactic acid. Now lactic acid may be formed out of sugar by means of a special organism inducing what is spoken of as the lactic acid fermentation. And we have every reason to believe that in even normal digestion, a certain quantity of sugar, either eaten as such, or arising from the amylolytic conversion of starch, does not pass away from the intestine into the blood as sugar, but undergoes this fermentation into lactic acid. To what extent this change takes place we do not know; the amount probably varies according to the amount of carbohydrates eaten, the condition of the alimentary canal, and other circumstances. It may be under certain circumstances simply a part of normal digestion; under other circumstances it may be excessive and give rise to troubles.

That fermentative changes may occur in the small intestine is further indicated by the facts that the gas there present may contain free hydrogen, and that chyme after removal from the intestine continues at the temperature of the body to produce carbonic acid and hydrogen in equal volumes. This suggests the possibility of the sugar of the intestinal contents undergoing the butyric acid fermentation during which, as is well known, carbonic anhydride and hydrogen are evolved. By this change the sugar is removed from the carbohydrate group into the fatty acid group; it is thus, so to speak, put on its way to become fat. We shall see hereafter that sugar may be somewhere in the body converted into fat; this conversion however takes place chiefly if not wholly in the tissues, and such change as may take place in the alimentary canal is to be regarded as suggestive rather than as important.

The hydrogen thus occurring in the intestine may also arise from the proteid decompositions spoken of above. However arising it may act as a reducing agent, reducing sulphates for instance, and thus giving rise to sulphides and to sulphuretted hydrogen; as a reducing agent it assists in the formation of the fæcal and urinary pigments.

Thus during the transit of the food through the small intestine, by the action of the bile and pancreatic juice, and possibly to some extent of the succus entericus, assisted by various micro-organisms, the proteids are largely dissolved and converted into peptone and other products, the starch is changed into sugar, the sugar possibly being in part further converted into lactic or other acids, and the fats are largely emulsified, and to some extent saponified. These products, as they are formed, pass into either the lacteals or the portal blood vessels, so that the contents of the small intestine, by the time they reach the ileo-cæcal valve, are largely but by no means wholly deprived of their nutritious constituents. So far as water is concerned, the secretion of water into the small intestine maintains such a relation to the absorption from it that the intestinal contents at the end of the ileum, though much changed, are about as fluid as in the duodenum.

In the Large Intestine.

§ **283**. The contents, whether alkaline or not in the ileum now become once more distinctly acid. This, however, is not caused by any acid secretion from the mucous membrane: the reaction of the intestinal walls in the large as in the small intestine is alkaline. It must therefore arise from acid fermentations going on in the contents themselves; and that fermentations do go on is shewn by the appearance of marsh gas as well as hydrogen in this portion of the alimentary canal. The character and amount of fermentation probably depend largely on the nature of the food, and probably also vary in different animals.

Of the particular changes which take place in the large intestine we have no very definite knowledge; but it is exceedingly probable that in the voluminous cæcum of the herbivora a large amount of digestion of a peculiar kind goes on. We know that in herbivora a considerable quantity of cellulose disappears in passing through the alimentary canal, and even in man some is digested. It seems probable that this cellulose digestion takes place in the large intestine, and is the result of fermentative changes carried out by means of micro-organisms, marsh gas being one of the products formed at the same time.

Be this as it may, whether digestion, properly so called, is all but complete at the ileo-cæcal valve, or whether important changes still await the chyme in the large intestine, one great characteristic of the work done in the colon is absorption. By the abstraction of all the soluble constituents, and especially by the withdrawal of water, the liquid chyme becomes as it approaches the rectum converted into the firm solid fæces, and the colour shifts from the bright orange, which the grey chyme gradually assumes after admixture with bile, into a darker and dirtier brown.

The Fæces.

§ 284. These consist in the first place of the indigestible and undigested constituents of the meal: shreds of elastic tissue, hairs and other horny elements, much cellulose and chlorophyll from vegetable, and some connective tissue from animal food, fragments of disintegrated muscular fibre, fat-cells, and not unfrequently undigested starch-corpuscles. The amount of each must of course vary very largely according to the nature of the food, and the digestive powers, temporary or permanent, of the individual. In the second place, to these must be added substances not distinctly recognisable as parts of the food but derived for the most part from the secretions of the alimentary canal. The fæces contain mucus in variable amount, sometimes albumin, cholesterin, butyric and other fatty acids, lime and magnesia soaps, colouring matters, and inorganic salts, especially earthy phosphates, crystals of ammonio-magnesia phosphates being very conspicuous. The reaction is generally but not always acid. They also contain a ferment similar in its action to pepsin, and an amylolytic ferment similar to that of saliva or pancreatic juice. The bile salts are represented by a small quantity of cholalic acid, or some product of that body, and sometimes a very small quantity of taurin. The glycin and most or all of the taurin have been absorbed from the intestine, and the cholalic acid has been partly absorbed and partly decomposed. The fact that the fæces become 'clay-coloured' when the bile is cut off from the intestine shews that the bile-pigment is at least the mother of the fæcal pigment; and a special pigment, which has been isolated and called stercobilin, is said to be identical with the substance called urobilin, which may be formed from bilirubin. As other special constituents of the fæces may be mentioned *excretin*, a somewhat complex nitrogenous body, whose exact chemical nature is at present uncertain, and *skatol* (C_9H_9N), a nitrogenous body which like indol is derived from the decomposition of proteids by means of micro-organisms, and which is the chief cause of the fæcal odour, since only a small quantity of indol remains in the fæces. These odoriferous bodies are derived directly from the food; at the same time it is quite possible that other specific odoriferous substances may be secreted directly from the intestinal wall, especially from that of the large intestine.

SEC. 9. THE LACTEALS AND THE LYMPHATIC SYSTEM.

§ 285. We have seen that absorption does, or at least may, take place from the stomach. We have also stated that a large absorption, especially of water, occurs along the whole large intestine. Nevertheless it is during the transit of food along the small intestine that the largest and most important part of the digested material passes away from the canal, partly into the lacteals, partly into the portal vessels. The portal vessels are simply parts of the general vascular system; the lacteals, into which we may at once say the greater part of the fat passes, are similarly parts of the general lymphatic system, being in fact the lymphatic vessels of the alimentary canal, and especially of the small intestine. The only reason for the special name of lacteals is that, unlike the lymphatic vessels of other parts of the body, the lymphatics of the intestine contain at times a fluid of a milky white appearance. Hence for the better understanding of absorption by the lacteals it will be desirable to study at some length the whole subject of the lymphatic system.

The lymphatic vessels may be said to begin in minute passages, possessing special characters, known as *lymph-capillaries.* Broadly speaking these lymph-capillaries are found, in the mammal, in all parts of the body in which connective tissue is found; and they have special connections with those minute spaces in connective tissue which we have already more than once spoken of as lymph-spaces. Of all the varied functions of connective tissue perhaps the most important is this relation to the lymphatic system; in nearly every part of the body connective tissue serves as the bed or origin of lymphatic vessels.

These lymph-capillaries, which, as we shall see, are frequently arranged in plexuses, are continuous with other passages also minute but of a different and more regular structure, the lymphatic vessels proper, which are gathered into larger and larger vessels, all running like the blood vessels in a bed of connective tissue, until at last all the lymphatic vessels of the body join either the great thoracic duct which opens by a valvular orifice into the venous system at the junction of the left jugular and subclavian veins, or the small right lymphatic trunk which similarly opens into the junction of the right jugular and subclavian veins. The latter course is taken by the lymphatics of the right side of the head and neck, the right arm, the right side of the chest, the right lung and the right side of the heart, as well as by some vessels coming from part of the upper surface of the liver; all the rest of the lymphatics including the lacteals fall into the thoracic duct.

The lymphatic vessels, while like the veins they join in their course into larger and larger trunks, do not increase in calibre so rapidly or so regularly as do the veins; they may run for some distance without greatly increasing in size; and further they, unlike the veins, freely anastomose, forming plexuses. Moreover during their course they enter into peculiar relations with structures known as lymphatic glands.

It will be advantageous to consider separately the lymphatic vessels other than the lymph-capillaries, the lymph-capillaries themselves, and the lymphatic glands.

The Lymphatic Vessels.

§ **286**. On these we need not dwell at length since their structure, in all essential respects, resembles that of the veins. The thoracic duct, which in man has at its lower end where it is widened into what is sometimes called the *receptaculum chyli* a diameter of six or seven millimetres, but is narrower higher up, may be said to possess three coats. The inner coat consists of a layer of fusiform epithelioid cells, not unlike those in a vein but more elongate and with a tendency to be sinuous in outline, and of a slender elastic lamina on which these rest. The middle coat consists of fine bundles of plain muscular fibres, which are for the most part disposed circularly but also to a certain extent obliquely and even longitudinally. The spaces between the bundles of muscular fibres are occupied by connective tissue and networks of elastic fibres. The outer coat, which is not well defined either from the middle coat on the one side or the connective tissue surrounding the duct on the other side, consists chiefly of connective tissue with elastic elements, a few muscular fibres being sometimes present. The wall of the thoracic duct is essentially muscular, and from the scantiness of connective tissue and of elastic elements is more tender, more apt to be torn than the wall of a vein of corresponding size. Numerous valves are present, these like the valves of the veins being foldings of the inner coat.

The smaller vessels resemble in structure the thoracic duct, the coats being of course more slender. In the majority of even smaller lymphatic vessels the muscular fibres are abundant.

Valves are especially numerous, and in many of the vessels, as for instance in those of the mesentery, just above each valve, where the tube is somewhat swollen, the muscular fibres, which elsewhere are chiefly disposed circularly, run in various directions so as to form a contractile network.

The smallest vessels, springing from the distinct lymph-capillaries to be immediately described, consist of hardly more than an epithelioid lining resting on a scanty connective tissue basis. The epithelioid cells are still fusiform and regular in shape, and the calibre of each vessel is fairly uniform though, owing to the valves which are exceedingly numerous, there is a great tendency to become beaded. These smaller vessels like the others also anastomose freely.

Lymph-Capillaries.

§ **287**. The smallest lymphatic vessels just described might, from analogy with the blood vessels, almost be considered as capillary vessels; but the name lymph-capillaries is given to vessels which joining and feeding those just described possess very different characters. They are on the whole larger in calibre than these, and distinctly larger than blood capillaries; they are exceedingly irregular in shape, and in their junctions with each other form irregular labyrinths rather than formal plexuses; they possess no valves and their only coat is an epithelium of a very striking character. Like the blood capillaries their structure is revealed by the action of silver nitrate. When a piece of tissue containing lymph-capillaries, ex. gr. one taken from the tendinous portion of the diaphragm, is examined after proper treatment with silver nitrate, numerous spaces, on the whole tubular but highly irregular in form, joining into an irregular labyrinth, are seen to be lined with a layer of epithelioid plates of a peculiar kind. Each plate or cell, which is more or less polygonal or at least not distinctly fusiform, is marked out by lines which are not straight and even, but very markedly sinuous, the several bulgings of one cell dove-tailing into the depressions of its neighbours and vice versa. Such epithelioid plates of sinuous outline, or such a sinuous epithelium, as we may for brevity's sake say, is characteristic of the lymph-capillaries. A lymph-capillary is in fact merely a space or areola of connective tissue, sometimes more or less tubular but frequently irregular in form, lined by a single layer of flat, transparent, nucleated epithelioid plates, each of which possesses a remarkably sinuous outline. The lymph-capillaries anastomose freely with each other and open into or join the smallest regular lymphatic canals, which, many of them smaller than the lymph-capillaries, are distinguished from these by their more regular disposition, by their epithelioid plates being fusiform with very little sinuosity of outline, and by the presence of valves.

The lacteal radicle of a villus (§ 262) is such a lymph-capillary, more or less tubular in form, or perhaps club-shaped and sometimes bifurcate or branched, placed by itself in the midst of the reticular tissue of the villus, ending, or as we should perhaps say beginning, blindly near the apex of the villus and joining below by a valvular mouth a regular lymphatic canal forming part of the network of regular lymphatic vessels with which as well as with lymph-capillaries the connective tissue of the mucous membrane is furnished.

In other parts of the body where connective tissue runs, lymph-capillaries are more or less abundant, all passing their contents on to the more regular lymphatic canals. In certain parts, as for instance in the central nervous system, the smaller blood vessels are surrounded by large lymph-capillaries, or by regular lymphatic vessels, in the shape of tubular sheaths. In these cases the lymph-capillary forms a sort of hollow jacket around the artery or vein which, covered with a layer of sinuous epithelioid plates, lies in the middle of a tubular space lined with similar sinuous plates. The plasma which exudes through the walls of the blood vessel passes accordingly at once into the tubular space or interior of the lymph-capillary, whence it is carried away into the regular lymphatic canals. Such an arrangement is spoken of as a "perivascular lymphatic."

§ 288. The lymph-capillaries may in one sense be regarded as the beginnings of the lymphatic system; they are the first lymphatic passages definitely lined with a continuous epithelium. But lymph exists outside these capillaries. In treating of connective tissue § 105 we more than once spoke of the spaces between the interlacing bundles of fibrillæ as lymph-spaces; and indeed they are during life occupied by fluid which may be spoken of as lymph. It is fluid which has in some way or other passed into them from the blood stream, through the walls of the capillaries and other minute blood vessels. We shall speak of this passage as a process of transudation and shall consider its nature later on. Many of the larger of these spaces, the areolæ of areolar connective tissue, are completely lined by epithelioid plates with sinuous outlines; these are in fact lymph-capillaries. But many spaces, especially the smaller ones, are not so lined; these lie outside the lymph-capillaries. Nevertheless they contain lymph, which reaching them by transudation through the walls of the blood vessels, streams from them in some way or other into the lymph-capillaries and so into the other lymphatic vessels. Coloured fluid injected by means of a fine syringe into these spaces soon finds its way into the lymphatics; and besides, in the vast majority of cases, a certain number of these spaces always intervene between the wall of the capillary or other small blood vessel from whence the lymph comes and the lymph-capillary to which the lymph goes; the lymph must have some means or other of passing from the spaces into the lymph-capillary. It is of course possible that the lymph transudes from the lymph-space into the lymph-capillary through the continuous sheet of epithelioid plates, in the same manner that it transudes from the blood-capillary into the lymph-space through the similarly continuous wall of the capillary; but there are some reasons for thinking that, at places. the epithelioid lining of a lymphatic capillary may be imperfect and so allow the interior of the lymph-capillary to open out into a connective-tissue space.

It will be remembered that, in the case of some of these spaces, a connective-tissue corpuscle may be found lying on the face of, or partly imbedded in, one of the bundles which form the walls of the space; and in some cases the space appears as it were imperfectly lined with scattered flat cells, which may perhaps be regarded as transitional forms between an ordinary branched connective-tissue corpuscle and a sinuous epithelioid plate. We may perhaps regard the epithelioid plate as a differentiated connective-tissue corpuscle, whose sinuosities of outline are the remains of its previously branched condition. If this be so we may consider the lymph-capillary as a differentiated connective-tissue space, and consequently may fairly expect that the one, if it does not as suggested actually open into, should be at all events in easy communication with the other. We seem justified at least in concluding that the completely lined lymph-capillaries draw their supply of lymph from the incompletely lined connective-tissue spaces.

We may probably go a step still further. Many of the connective-tissue corpuscles are imbedded in, lie in cavities excavated out of, the cement substance which unites the fibrillæ into bundles and sometimes joins the bundles together; in some situations the corpuscles are similarly imbedded in a homogeneous ground substance which has not become differentiated into fibrillæ. The cavities in which these corpuscles lie are, like the corpuscles themselves, branched and generally flattened; they appear moreover to be generally larger than the corpuscles so as to leave a small space which can be occupied by fluid. Where two corpuscles lie near each other their spaces may, by means of the branches, communicate; and in some situations, as in the body of the cornea where a number of flattened corpuscles are imbedded in the lamina of ground substance which unites each two adjacent parallel (or rather concentric) laminæ of fibrillated bundles, the series of cavities, uniting by their branches may be regarded as constituting a labyrinth of passages, largely but not entirely filled by the corpuscles, space being left for some amount of fluid. That fluid we need hardly say is lymph. And though the view is not one admitted on all hands, there are reasons of some weight for thinking that these cavities belonging to the corpuscles open out into the connective-tissue spaces just treated of or even more directly into the lymph-capillaries. When a piece of connective-tissue, such for instance as that lying between the radiating bundles of the tendon of the diaphragm on the pleural side is treated in a particular way, the result is what is called a "negative staining"; the matrix is stained brown but the corpuscles and cavities are left unstained, and appear as irregularly branched clear patches standing out in contrast with the brown matrix. In such a preparation many of these clear spaces are seen to abut upon and apparently to lose themselves in a neighbouring lymph-capillary, which also always stands out in contrast to the matrix, appearing as a clear space marked with the sinuous outlines of its plates.

Without insisting too much on the argument drawn from this negative staining, and resting rather on the facts previously mentioned and on general considerations, we may probably conclude that all the spaces of connective-tissue, including the cavities of the corpuscles, form a labyrinth of passages which is to be considered as the real beginning of the lymphatics, and that this irregular labyrinth is in some way or other in fairly free communication with the more regular but still labyrinthine lymph-capillaries, lined by a definite epithelioid lining, and that from thence the lymph passes on to the regular and valved lymphatic canals.

All over the body wherever blood vessels go connective-tissue and lymph-spaces go too. Certain parts of the plasma of the blood passing through the walls of the blood vessels become lymph in these lymph-spaces. As such it soaks through not only the bundles of gelatiniferous fibrillæ of the connective-tissue itself, but also the basement membrane and so the epithelium of the mucous membrane and its glands, the unstriated muscular fibre, the sarcolemma and muscle substance of the striated fibre, the neurilemma and contents of the nerve-fibre of nerves, in fact the elements of all the tissues which are supplied with blood vessels. More than this, lymph goes where blood vessels do not go, and in these situations the value as lymph-passages of the cavities of the corpuscles seems most striking. In the cornea for instance blood vessels and definitely constituted lymphatic vessels cease near the periphery, and the greater part of the nutrition of the cornea (beyond that effected by what we may call mere imbibition, that is by the passage of fluid between the molecules of the actual substance of the tissue) is carried on by the stream of lymph through the corpuscular cavities. In a similar way in bone lymph finds its way from the blood vessels of the periosteum, marrow and Haversian canals through the very substance of the bone by means of the labyrinth of lacunæ and canaliculi. And in cartilage we have reason to think that minute passages in the matrix facilitate the transmission of lymph from the perichondrium through the body of the cartilage from cartilage cell to cartilage cell, far more efficiently than if its progress were left to mere imbibition. The somewhat peculiar relations of the lymphatics in the central nervous system we shall consider when we come to treat of that system. Meanwhile we have said enough to form a general idea of the arrangements by means of which the very elements of all the tissues are bathed with lymph, and by means of which that lymph is carried back from the elements of the tissues along irregular and regular lymphatic channels back to the blood from whence it originally came.

§ **289**. *The Serous Cavities.* In the mammal lymph-spaces are for the most part minute and microscopic; but in some other animals they may attain considerable size; in the frog for instance in which lymph-capillaries and lymphatic vessels are scanty, the large subcutaneous spaces which are disclosed when the skin of the back is cut through are in reality lymph-spaces lined by sinuous epithelioid plates. Both in the mammal and other animals certain large cavities, known as serous cavities, such as the peritoneal, pericardial, pleural and other cavities, must be considered as parts of the general lymphatic system, and indeed the 'serous fluid' which they contain is in reality lymph. The subarachnoid space surrounding the brain and spinal cord may also perhaps be regarded as a part of the lymphatic system, but this and the contained cerebro-spinal fluid we shall consider in connection with the central nervous system.

In the abdomen of the frog, on each side of the vertebral column, behind or above, *i.e.* dorsal to the peritoneal cavity, lies a large lymph-space spoken of as the *cisterna magna lymphatica*, the cavity of which is separated from the peritoneal cavity by a thin membranous sheet consisting of a median basis of connective-tissue covered on the peritoneal side by peritoneal epithelium and on the cisterna side by lymphatic epithelium. The latter consists, as in a lymphatic capillary, of flat epithelioid plates with sinuous outlines; the former is made up also of flat epithelioid plates but these are more or less polygonal in shape and have outlines which are not distinctly sinuous. If a piece of this partition, after being stained with silver nitrate, be spread out and examined either with the peritoneal or with the cisterna side uppermost, it will be seen that in each case here and there a group of cells assuming a triangular form appear to converge to or radiate from a centre which sometimes, especially on the lymphatic side, is a mere point but sometimes is a larger or smaller hole, which in other words is an orifice or *stoma*, sometimes closed but sometimes more or less open. On the peritoneal surface the stoma is surrounded and guarded by a crown of what appear to be small granular cells placed at the apices of the converging epithelioid plates, but which are held by some to be the displaced nuclei of the epithelioid plates themselves. Around each stoma which is in reality a perforation leading from the peritoneal cavity into the cisterna, the connective-tissue basis between the two epithelioid layers is arranged in a concentric manner; the whole arrangement serves as a communication from the peritoneal cavity into the cisterna, and by these stomata the peritoneal fluid passes into the cisterna and so into the general lymphatic system. Owing to causes which we shall study presently the contents of the small lymphatic vessels and such spaces as the cisterna are continually being drained by the vascular system; the cisterna is continually tending to empty itself and so to draw fluid from the peritoneal cavity through the stomata. In the female frog the small granular cells encircling the stomata are, during the breeding season provided with cilia, the action of which increases the current from the peritoneum through the stoma into the cisterna.

In the mammal similar stomata place the serous cavities in connection with the lymphatics of the walls of those cavities. They may be readily seen in the tendon of the diaphragm. The peritoneal membrane of the mammal as of the frog consists of a single layer of flat epithelioid plates lying on a connective-tissue basis; the plates, smaller than those in the frog, are polygonal in form, and their outline is not sinuous. On the tendon of the diaphragm the epithelioid plates over the radiating spaces, or clefts between the radiating bundles of the tendon, are smaller than over the bundles themselves, and along the lines of these radiating intertendinous spaces may be seen stomata, orifices guarded by small cells, similar to but smaller than and less conspicuous than those just described as seen in the frog. These stomata open into the lymphatics which are abundant in the connective tissue lying between the radiating bundles of the tendon of the diaphragm, and through them the fluid of the peritoneal cavity passes away into the lymphatics of the diaphragm and so into the general lymphatic system. The movements of the diaphragm in breathing, of which we shall have to speak presently, greatly assist the flow through the stomata; and even passive movements of the diaphragm are effectual for this purpose. If a quantity of injection material, such as a solution of Berlin blue, be injected into the peritoneal cavity of a living animal it soon enters into and injects the lymphatics of the diaphragm, and a similar injection may be obtained in a dead but recently killed animal by placing the animal with its head downwards, injecting the colouring matter into the abdomen, or even pouring it into the hollow of the diaphragm, and then producing movements of the diaphragm by a rhythmically repeated artificial respiration. Not only coloured fluids but coloured material merely suspended in fluid and such things as the globules of fat in milk, or even red blood corpuscles may thus find their way from the peritoneal cavity into the lymphatics of the diaphragm. Indeed if a piece of the diaphragm of a recently killed animal be stretched out and milk poured upon it, the fat globules of milk may be seen with the aid of a lens or microscope to disappear through the stomata in a number of minute vortices.

By similar stomata the pleural cavity is put into communication with the lymphatics not only of the diaphragm (on its pleural surface) but also of the lungs, and to a smaller extent of the thoracic walls, and during the movements of the chest in breathing the contents of the pleural cavity are continually being pumped away, partly into the lymphatics of the lungs partly into those of the diaphragm and chest walls. In a similar manner pericardial fluid passes away from the pericardial cavity, and the fluid in other smaller serous cavities such as that surrounding the testis, passes away from the respective cavities into the general lymphatics. The quantity of fluid in even the largest of these cavities is at any one time in normal conditions very small, but that fluid appears to be continually renewed, old fluid passing away to the lymphatic system, and new fluid taking its place. The serous cavities therefore are to be regarded as expanded initial reservoirs from which as well as from the lymph-capillaries and lymph-spaces of the tissues the lymph stream is continually being fed.

The Structure of Lymphatic Glands.

§ 290. *Solitary Follicles and Peyer's Patches.* All along the small intestine and at various points of the circumference are found, partly in the submucous tissue but reaching up to the surface of the mucous membrane, small rounded bodies, of the size of a small pin's head, more numerous perhaps in the lower than in the upper part of the bowel, often called 'solitary glands.' They are not glands however in the sense (§ 209) of being involutions of the mucous membrane, and it is better perhaps to speak of them as *solitary follicles.* At the free border of the small intestine, opposite to the attachment of the mesentery, the mucous membrane contains long oval patches, Peyer's patches, placed lengthways, there being some twenty or thirty of these; they are most numerous in the ileum and disappear towards the duodenum. Each patch is practically a group of solitary follicles, and indeed these patches are sometimes spoken of as *agminated follicles.* In the large intestine especially at the cæcum, and in man particularly in the vermiform appendix, solitary follicles are abundant, but here they lie wholly in the submucous tissue below the muscularis mucosæ. In the stomach also, in young people, there occur in the mucous membrane, generally between the mouths of the glands, structures which are very similar to solitary follicles and which are sometimes called "lenticular glands."

A solitary follicle consists essentially of a spherical mass of fine adenoid tissue the meshes of which are crowded with leucocytes. In the intestine as we have seen (§ 259) the connective tissue lying between the epithelium above and the muscularis mucosæ below has a reticular arrangement and contains leucocytes; but in the follicle the network is finer, closer and more regular than elsewhere, the meshes are almost completely filled with leucocytes, and the spherical mass breaking through the muscularis mucosæ reaches some way down into the submucous tissue. Over the surface of the follicle, which bulges somewhat into the interior of the intestine, villi may be present, but the glands of Lieberkühn are pushed aside and are found only at its circumference. Into this mass of adenoid tissue one or more small arteries enter and break up into a capillary network the blood from which is carried away by one or more small veins. Around the mass there is placed a more or less well developed spherical lymph space, lined with sinuous epithelioid plates and continuous with the neighbouring lymphatic vessels. This lymph space or *lymph-sinus* as it is called thus forms a hollow jacket filled with lymph round the spherical mass of adenoid tissue, but is not complete, being broken by the entering and issuing blood vessels, or by imperfect partitions passing from the tissue without to the adenoid tissue within. The blood vessels and bridles in question are covered by a layer of epithelioid plates continuous with that lining the outer wall of the jacket, as also with the one which more or less completely invests the inner mass of adenoid tissue.

The leucocytes which occupy the meshes are of different sizes. Some are as large or almost as large as white blood-corpuscles, from which indeed they chiefly differ in the fact that their nuclei exhibit a nuclear network which as we have seen (§ 28) is apparently not present in the white corpuscle of the blood. The majority however are much smaller than white blood corpuscles, their smallness being chiefly due to the small amount of cell-substance surrounding the nucleus; in some only a mere film of cell-substance can be detected so that the nucleus appears almost as a so-called ‘free’ nucleus. Many of the leucocytes may be seen to be undergoing karyomitosis, indicating that they are multiplying by division; and indeed there are many reasons for thinking that in the adenoid tissue of these follicles and other similar structures a very considerable multiplication of leucocytes takes place. Many of the leucocytes of these follicles exhibit under favourable circumstances amœboid movements, and the smaller leucocytes, indeed even the smallest, seem at times as active as the larger ones.

A solitary follicle then may be considered as consisting in the first place of a rounded capillary network fed and drained by small arteries and veins, all supported by a minimal amount of ordinary connective tissue. In the second place the interstices of this vascular network are filled up with adenoid tissue the fine meshes of which are crowded with leucocytes of variable but on the whole small size. Lastly the rounded mass thus constituted is surrounded by a lymph sinus, the fluid of which on the one hand bathes the mass and on the other hand is free to pass away into the neighbouring lymphatic canals. As the blood streams through the capillary network part of the plasma passing through the capillary walls becomes lymph in the meshes of the adenoid tissue. Hence, after probably acting on and being acted on by the leucocytes, it passes into the lymph sinus and so away into the general lymphatic stream. In all probability the lymph sinus is chiefly filled from the fluid thus coming from the adenoid tissue, so that a main current flows from the lymph sinus into neighbouring lymphatics in all directions; but it may be that the lymph sinus is partly supplied by the lymphatics around, so that some of the lymph from adjoining structures, while flowing in the sinus around the adenoid tissue, is subjected to the action of that tissue. In all probability too the transit of material from the blood to the adenoid tissue is accompanied by a reverse current from the adenoid tissue to the blood, so that the blood in passing through the follicles not only gives but also takes.

Since multiplication of leucocytes appears to be continually going on in the adenoid tissue and since the follicles do not increase indefinitely in size some of the leucocytes must disappear. There is every reason to think that they pass away into the lymph sinus and so joining the general lymph stream become the corpuscles of the lymph of which we shall presently speak. If the central adenoid mass is, as some think, invested with a continuous coat of sinuous epithelioid plates, the leucocytes which leave the follicle must pass through the coat in the same manner that the white corpuscles of the blood migrate through the walls of the blood vessels; but it is more probable that, as others think, the coating is discontinuous, the spaces of the adenoid tissue opening freely at intervals into the lymph sinus, and thus affording an easy path not only for the leucocytes but also for the fluid.

The lenticular glands of the stomach appear to be only less condensed, less completely arranged masses of adenoid tissue; and as we shall see hereafter small masses of adenoid tissue more or less condensed, more or less transformed into definite follicles are met with in various parts of the body.

§ 291. *A Peyer's Patch* is, as the phrase "agminated gland" indicates, merely an aggregation of solitary follicles. A well formed Peyer's patch consists of a variable number, in man fifty or even a hundred or fewer, of solitary follicles arranged in a single layer close under the epithelium, but stretching down into the submucous tissue, the distinction of which from the mucous membrane proper is to a great extent lost by the breaking up of the muscularis mucosæ. Between the constituent follicles glands of Lieberkühn are found encircling the follicles, and villi project from the surface, while between and below the glands blood vessels and lymphatics are abundant. Over each follicle both glands and villi are absent so that the upper surface of the follicle is in contact with the epithelium of the intestine, which is here shorter and more cubical than elsewhere.

Each follicle consists of a somewhat spherical vascular mass of adenoid tissue surrounded more or less completely by a lymph sinus; in fact the structure of each of these aggregated follicles repeats so completely that of a solitary follicle that the same description and discussion will serve for both.

§ **292**. *Lymphatic glands.* If the structure of a follicle just described be borne in mind, that of a lymphatic gland is made more easy; for, as a Peyer's patch is a mere aggregation of otherwise unchanged follicles, so a lymphatic gland is a collection of similar follicles differentiated into a compact and somewhat complex organ.

A typical lymphatic gland has, though the form varies a good deal, the shape of a kidney, in so far at all events that a more or less convex side can be distinguished from a concave side in which is placed the hilus where the blood vessels enter and issue; from the hilus also issue lymphatic vessels, which since they carry lymph away from the gland are called efferent lymphatics. The afferent vessels carrying lymph to the gland pass into the gland in a scattered fashion on the convex side.

The gland is invested by a capsule of connective tissue, containing in the case of many animals a very considerable number of plain muscular fibres. Two layers may at times be distinguished in the capsule: an outer layer of coarser and an inner layer of finer connective tissue, a rich plexus of lymphatic vessels being placed between the two. From the capsule a number of partitions or *trabeculæ,* starting from various points of the surface and consisting, like the capsule, of closely interwoven bundles of connective-tissue mixed up with a variable number of plain muscular fibres, pass into the gland in a direction converging towards the hilus. In the outer or circumferential part of the gland these trabeculæ are large, run in a straight direction, are but little branched, and are so arranged that they cut up the outer part of the gland into a number of chambers, having more or less the form of truncated pyramids, converging to or radiating from the inner portion of the gland near the hilus. These chambers have been called *alveoli,* and constitute together the *cortex* of the gland, the inner portion being called the *medulla.* On reaching the medulla the trabeculæ, the course of which as we have just said is in the cortex on the whole straight and unbranched, rapidly divide becoming thinner and more slender and, running and joining together in all directions, form an irregular open network giving rise to a labyrinth of passages into which the alveoli of the cortex open.

The trabeculæ in fact starting from the capsule divide the gland into a number of spaces which in the cortex are arranged in a regular manner and have the form of converging chambers or alveoli, communicating laterally with each other to a small extent only, but which in the medulla rapidly diminish in size and, opening freely into each other on all sides, form a labyrinth. At the hilus the medulla comes to the surface of the gland, but elsewhere is separated from the surface by the cortex. The number of and regularity of division among the alveoli, and the sharpness of distinction between the cortex and the medulla differ in the glands of different animals.

Each alveolus of the cortex consists in its central part, constituting about two-thirds or more of the whole chamber, of a mass of adenoid tissue crowded with leucocytes; this mass which follows the form of the chamber, is wholly like, in fact repeats almost exactly the structure of the mass of adenoid tissue of a solitary follicle of the intestine; it is spoken of as the *follicular* or *glandular substance* or more briefly the *follicle*, of the alveolus. This follicle is separated on all sides from the capsule and trabeculæ which form the walls of the alveolus (or from the trabeculæ alone where as in some cases the alveolus is a small one lying between the larger superficial alveoli and the true medulla) by a space which is occupied as a rule not by true adenoid tissue but by a coarser more open reticular tissue, the meshes of which are larger and less regular and the bars of which are more membranous, having more the characters of being branches of nucleated branched-cells than, as we have seen, is the case with true adenoid tissue. The meshes of this reticulum like those of adenoid tissue are occupied by leucocytes; but these are not so numerous, and moreover more readily escape from this situation than from the follicles, so that when a section of a fresh gland is brushed with a camel's hair pencil or shaken up in normal saline solution, the spaces of which we are speaking are to a large extent cleared of the leucocytes previously present, while the follicular substance still remains crowded with them. After treatment with silver nitrate it is seen that the surface of the trabeculæ (and capsule) bordering this space in each alveolus is lined with sinuous epithelioid plates, and a coating of similar plates may sometimes be made out on the surface of the follicular substance. In other words this space between the trabeculæ and the follicular substance is a lymph-space corresponding to the lymph sinus of the solitary follicle of the intestine, and indeed is spoken of as the *lymph sinus* or *lymph channel;* the lymph sinus of an alveolus of a lymphatic gland differs from the lymph sinus of a solitary follicle of the intestine in its space being much broken up by reticular tissue.

The irregular passages of the medulla are similarly occupied by a central mass of follicular substance surrounded by a lymph sinus; but, whereas in the alveoli the masses of follicular substance take on the form of more or less pyramidal blocks, in the medulla the follicular substance is arranged in the form of branching and anastomosing cords, *the medullary cords*, surrounded by a tubular branching and anastomosing jacket of lymph sinus. At the junction of the cortex and medulla the follicles of the alveoli of the former branch off into and become the medullary cords of the latter, and the lymph sinuses of the former are similarly continuous with the labyrinth of lymph sinuses of the latter.

The gland in fact may be considered as consisting of three parts:—the skeleton supplied by the capsule and trabeculæ and dividing the interior of the gland into the regular alveoli of the cortex and the labyrinth of the medulla; the follicular substance occupying the centre both of the alveoli and of the labyrinth and continuous throughout both, as if it had originally filled up the whole of the spaces of the skeleton and had subsequently shrunk away on all sides; and lastly the lymph channel occupying all the spaces left between the follicular substance and the skeleton, and thus forming a labyrinth of its own throughout the gland. Obviously a lymphatic gland is a consolidated and differentiated collection of lymphatic follicles or Peyer's patch. In a Peyer's patch each follicle is distinct and independent; in a lymphatic gland the follicles are fused together, partially so in the cortex but completely so in the medulla.

The afferent lymphatic vessels, which are small or medium sized vessels with the structure described in § 286, after forming a plexus between the two layers of the capsule open out into the lymph sinuses of the alveoli beneath the cortex; these lymph sinuses are practically lymph-capillaries into which the regular afferent lymphatic vessels break up. The efferent lymphatic vessels are similarly connected with the lymph sinuses of the medulla at the hilus; here the lymph-capillaries of the medulla open into and form the regular lymphatic vessels which issue from the gland at this point. In the afferent vessels the lymph is flowing as we shall see, at a certain rate and under a certain pressure; it continues to flow through the labyrinth of the lymph sinuses of the gland, bathing as it flows the follicular substance, its course being retarded by the reticulum of the lymph sinuses; it finally issues by the efferent vessels.

The small arteries entering the gland at the hilus run along the skeleton of trabeculæ, dividing as they go; at intervals they send off small branches which, leaving the trabecular support, traverse the lymph sinus and plunging into the follicular substance break up into capillaries. By far the greater part of the blood sent to the gland thus runs in capillary networks in the follicular substance of the alveoli and medulla. From these capillaries the blood finds its way back by veins through the lymph sinus to the trabeculæ, and so issues from the gland at the hilus.

§ 293. Obviously here, as in the lymphatic follicle of the intestine, the adenoid tissue, or follicular substance, is the seat of an interaction between the blood and the lymph; here the blood gives something to and takes something from the lymph, or at least is in some way changed; here the lymph takes from and gives up to the blood. We may be confident that these changes take place, though our knowledge as to the exact nature of these changes is at present very limited.

One event taking place in the gland seems tolerably certain. The leucocytes which occupy the meshes of the follicular substance, and the characters of which are similar to those of the leucocytes of a follicle of the intestine, multiply in the follicular substance. Cell-division appears to be particularly active in, but not exclusively confined to, certain areas in the follicles spoken of as *lymph-knots*. In nuclear-stained sections, that is in preparations so treated that while the nuclei are stained deeply the cell bodies are very lightly stained or not at all, there may be frequently seen in a follicle an area (or more than one area) consisting of a very light centre surrounded by a deeply stained ring. In the light centre the cell bodies of the leucocytes are, relatively to the nuclei, larger than in the surrounding zone; and since the cell bodies are not stained the central portion appears lighter. It is in the clearer central area that nuclei undergoing mitosis, and indicating cell division, are especially abundant. The surplus cell population thus arising appears to pass, chiefly at all events, into the lymph sinus, and to leave the gland by the efferent lymphatic vessels; on examination it is found that lymph which has passed through a number of glands is richer in lymph corpuscles than the lymph which is coming to the glands.

Many lymphatic glands contain a quantity of black pigment which is chiefly deposited in the branched cells of the reticulum of the lymph sinuses. This is probably, in many cases at all events, pigment brought to the gland in the lymph vessels, and arrested in its course through the lymph sinus; and in the bronchial lymphatic glands the pigment simply consists of minute particles of carbon introduced into the bronchial passages by the inspired air, and carried from the bronchial passages to the glands. In some cases, however, pigment is also found in the bodies of the leucocytes of the follicular substance, and this pigment has probably a different origin; its history and purpose are not however as yet known.

SEC. 10. THE NATURE AND MOVEMENTS OF LYMPH (INCLUDING CHYLE).

§ **294**. From what has been said in the preceding section we are led to regard the multitudinous spaces, both small and great, of connective tissue all over the body, including among these the "serous cavities," as forming the beginning or roots of the lymphatic system. Into these spaces certain parts of the plasma of the blood transude and so become lymph ; (whether the epithelioid lining of the large serous cavities plays any distinct part in regulating the transudation of serous fluid, i.e. of lymph into those cavities we do not know); from these spaces the lymph is continually flowing through the lymph-capillaries into the lymphatic vessels, and so by the thoracic duct and right lymphatic trunk back into the blood system.

The amount of lymph occupying the lymph spaces, lymph capillaries, and minute lymphatic vessels of any region varies from time to time according to circumstances. A hand for instance which has been kept hanging down for some time becomes swollen and the skin tense ; if it be raised the swelling lessens and the skin becomes loose ; and a similar temporary swelling of the skin of the limbs, and of the skin generally, is frequently the result of active exercise. Such a swelling is partly due to the blood vessels being dilated, or to the return flow along the veins being retarded so that the blood capillaries become distended with blood, but is much more largely owing to the lymph-spaces and lymphatic vessels of the skin and underlying structures being unusually filled with lymph. On the other hand the skin may become shrivelled and dry from a deficiency of lymph in the lymph-spaces and vessels. Under even normal circumstances the quantity of lymph in the tissues may vary considerably, and under abnormal circumstances a very large amount of lymph may greatly distend the spaces of the connective tissue of the skin and other structures, giving rise to *œdema* or dropsy. Obviously there are agencies at work in the body by which the appearance of lymph in the spaces or its removal thence along the lymph-channels, or both, may be either increased or diminished.

The Characters of Lymph.

§ **295**. As it slowly flows from its origin in the tissues to the mouth of the thoracic duct (we may for simplicity's sake omit the right lymphatic trunk) the lymph is subjected to the influence of the lymphatic glands, and is possibly affected by the walls of the lymph-vessels. Moreover the lymph coming from one tissue differs more or less in certain characters from the lymph arising in another tissue, just as the venous blood of one organ differs from the venous blood of another organ; and these differences may be exaggerated by the activity of the one or other tissue. Of these differences by far the most striking is that between the lymph coming from the alimentary canal during active digestion and known as *chyle*, and the lymph coming from other parts of the body. When digestion is not going on, and when consequently no considerable absorption of material from the alimentary canal into the lacteals is taking place, the fluid flowing along the lacteals is lymph, not differing from the lymph of other regions to any marked degree.

The fluid accordingly which flows along the thoracic duct in an animal which has not been fed for some considerable time may be taken as illustrating the general characters of lymph. The contents of the thoracic duct may be obtained by laying bare the junction of the subclavian and jugular (in the dog the junction of the axillary and jugular) veins, and introducing a cannula into the duct as it enters into the venous system at that point. The operation is not unattended with difficulties.

Lymph, so obtained, is a clear transparent or slightly opalescent fluid, which left to itself soon clots. The clotting is not so pronounced as that of blood, but clotting is caused as in blood by the appearance of fibrin. The fibrin which is formed though scanty, ·05 p.c., is identical apparently with that of blood, and as far as we know, all that has been said previously, §§ 14—23, concerning the nature of clotting in blood applies equally well to lymph.

Examined with the microscope lymph contains a number of corpuscles, lymph-corpuscles, which in all their characters as far as is at present known are identical with white blood corpuscles; they vary in size from 5 μ to 15 μ, and the smaller corpuscles are much more abundant in lymph than in blood. Like the white blood corpuscles of blood they exhibit amoeboid movements. Their number varies in different animals, and, apparently, in the same animal, according to circumstances; on the whole perhaps it may be said that lymph corpuscles are about as numerous in lymph as white corpuscles in blood. Even when every care is taken to avoid admixture with blood, lymph, and especially chyle, not unfrequently contains a certain number of red blood corpuscles; sometimes these are sufficient to give the lymph (or chyle) a reddish tinge. They have been observed within the living lymphatic vessels, even within small ones, and have probably in some manner or other made their way from the blood into the lymph channels.

§ **296**. The chemical composition of lymph, even when taken in each case from the thoracic duct, varies a good deal. The total solids are much less than in blood, amounting in general to not more than 5 or 6 p.c. Hence the venous blood of a vascular area contains rather more solids than the arterial blood of the same area, since the blood in giving rise to the lymph during its passage through the capillaries from the arteries to the veins has parted with relatively more water than solid matter.

The proteids amount on the average to about 3 or 4 p.c., that is to say, to about half as much as in blood, the particular proteids present being the same as in blood, viz. albumin, paraglobulin and antecedents of fibrin. In lymph, as distinguished from chyle, the quantity of fat is small, and consists of the usual neutral fats and the soaps of their fatty acids, together with lecithin; cholesterin may also be present. A certain amount of sugar (dextrose) appears to be always present, and several observers have found an appreciable quantity of urea. The ash of lymph like that of blood serum contains a considerable quantity of sodium chloride, while phosphates and potash are scanty; it also contains iron, apparently in too great a quantity to be accounted for by the few red corpuscles which may be present. From lymph a certain amount of gas can be extracted, consisting chiefly or almost exclusively of carbonic acid, with a small quantity of nitrogen, the amount of oxygen present being exceedingly small. The importance of this we shall see when we come to study respiration.

Broadly speaking we may say that all the substances present in blood-plasma are present also in lymph, but are accompanied by a larger quantity of water.

§ **297**. Lymph may also be obtained from separate regions of the body, as from the lower or upper limbs, for instance, by introducing a fine cannula into a lymphatic vessel. In its general features the lymph so obtained resembles that taken from the thoracic duct. Analyses of the lymph distending the subcutaneous connective tissue in cases of dropsy shew that this contains much less solid matter than normal lymph taken from the thoracic duct or larger lymphatic vessels. From this it has been inferred that the lymph normally existing in the lymph-spaces, lymph-capillaries and minute vessels contains an excess of water; and indeed it has been asserted that the per-centage of solids increases in passing from the smaller to the larger vessels; but this cannot be regarded as distinctly proved. The number of corpuscles however, as we have already said, appears to be increased in passing through the lymphatic glands. It has also been stated that the lymph in the finer lymph-vessels clots even less firmly than that in the thoracic duct. From this we may infer that some of the leucocytes in the adenoid tissue of the follicles of a lymphatic gland find their way into the lymph-sinus, and so into the efferent lymphatics, and that some of the fibrin factors are added to the lymph, or at least that some changes favourable to clotting are brought about.

§ **298**. We shewed in § 289 that the large serous cavities of the peritoneum, pericardium &c. were to be considered as parts of the lymphatic system, and that the 'serous fluid' in these cavities was continually joining the lymph stream; indeed pericardial or other serous fluid has all the general characters of lymph. We have already said, § 20, that these fluids when taken fresh from the body, clot (this is, at least, the case in most animals); the clot when examined microscopically is found to consist of colourless corpuscles like those of lymph or of blood entangled in the meshes of fibrin. Both in their proteid and other chemical constituents these serous fluids resemble lymph. Analyses of the accumulations of fluid occasionally occurring in these cavities shew that they contain sometimes less and sometimes more solid matter than ordinary lymph. The aqueous humour of the eye contains very little solid matter; and the cerebro-spinal fluid is so peculiar that it had better be considered by itself in connection with the nervous system.

§ **299**. *Chyle.* In fasting animals the fluid flowing along the lacteals, as may be seen by inspection of the mesentery, is clear and transparent; it is lymph, differing as we have said, in no essential respects from the lymph flowing along other lymphatic vessels. Shortly after a meal containing fat (and every meal does contain some fat), the lymph becomes white and opaque like milk, the more so the richer the meal is in fat; it is then called *chyle.* Owing to the relatively large quantity of this milky fluid which for some time after a meal continues to be poured into the thoracic duct, the contents of that duct also become milky, and are also called chyle. In the thoracic duct the chyle of the lacteals is more or less mixed with lymph from other lymphatic vessels, but the former is so preponderating that the contents of the duct may be taken as illustrating the nature of chyle.

Chyle differs from lymph in one important respect, and one only: whereas lymph ordinarily contains a small quantity only of fat, chyle contains a very large amount. The actual amount of fat present in the chyle of the thoracic duct varies, as may be expected, very considerably, according to the nature of the meal, the stage of digestion, and various circumstances. Five per cent. is a very common amount; in the dog it has been found to vary from 2 to 15 per cent. The increase in fat is chiefly if not exclusively due to an increase in the neutral fats; though whether the small quantity of soaps and of lecithin present is greater than in lymph has not been distinctly ascertained. Cholesterin is probably present in greater amount than in lymph, since it probably comes from the bile poured into the intestine during digestion; but this is not certain. How far the nature of the fat, that is, the proportion of the various kinds of fat, of stearin, &c., varies with the fats present in the meal has not been definitely ascertained.

The condition of the fat in chyle is peculiar. Some of it exists, like the fat in milk, in the form of fat globules of various sizes, but all small. A very considerable quantity however is present in the form of exceedingly minute spherules or granules, far smaller than any globules to be seen in milk; these exhibit active 'Brownian movements.' The fat present in this form is spoken of as the 'molecular basis' of chyle, and is very distinctive of chyle. In the emulsified contents of the intestine, often called chyle, the fat is finely divided, and to a large extent into small globules, but there is nothing corresponding to this molecular basis; the fat does not assume this condition until it has passed out of the intestine into the lacteals. Lymph examined with the microscope shews besides the white corpuscles only very few oil-globules, and nothing of this molecular basis. Just as in fact lymph is, broadly speaking, blood *minus* its red corpuscles, so chyle is lymph *plus* a very large quantity of minutely divided neutral fat.

The total amount of lymph or of chyle which enters the blood system through the thoracic duct, though it probably varies considerably, is probably also always very large. It has been calculated that in a well-fed animal a quantity equal at least to that of the whole blood may pass through the thoracic duct in 24 hours, and of this it is supposed that about half comes through the lacteals from the alimentary canal, and therefore to a large extent from food, and the remainder from the body at large. These calculations are based on uncertain data, and cannot therefore be taken as of exact value, but we may use them for the sake of an illustration. Thus in a man of average weight, that is, about 154 kilos., the quantity of blood (§ 38) being $\frac{1}{13}$ of the body weight is about 12 kilos. The quantity of lymph or chyle therefore discharged into the blood in an hour would be according to this calculation half a kilo, or something less than half a litre; and since the flow must vary considerably in the 24 hours, would be sometimes less and therefore sometimes even more than this.

The Movements of Lymph.

§ **300**. Making every allowance for the uncertainty of the calculation detailed in the preceding paragraph, it is obvious that the lymph must flow with a not inconsiderable rapidity (if we take about half the above estimate, the rate will be about 5 c.c. per minute) through the thoracic duct, and therefore must also be continually streaming into that duct, along the various lymphatic channels from the manifold lymph-spaces of the body. This onward progress of the lymph is determined by a variety of circumstances. In the first place, the remarkably wide-spread presence of valves (§ 286) in the lymphatic vessels causes every pressure exerted on the tissues in which they lie to assist in the propulsion forward of the lymph. Hence all muscular movements increase the flow. If a cannula be inserted in one of the larger lymphatic trunks of the limb of a dog, the discharge of lymph from the cannula will be more distinctly increased by movements, even passive movements, of the limb than by anything else. When we come to speak of the entrance of chyle into the lacteal radicles of the villi we shall see that, at all events according to one view, the muscular fibres of the villus act as a kind of muscular pump, driving the chyle past the valved end of the lacteal radicle into the lymphatic canals below. In addition to the presence of valves along the course of the vessels, the opening of the thoracic duct into the venous system is guarded by a valve, so that every escape of lymph or chyle from the duct into the veins becomes itself a help to the flow. In the second place, we have already seen that the blood-pressure in the capillaries and minute vessels is considerably greater than that in the large veins, such as the jugular; in fact this difference of pressure is the cause of the flow of blood from the capillaries to the heart. Now the lymph in the lymphatic spaces outside the capillaries and minute vessels undoubtedly stands at a lower pressure than the blood inside the capillaries; otherwise the transudation from the blood into the tissues would be checked; but the difference is probably much less than the difference between the pressure in the capillaries and that in the large venous trunks. So that the lymph in the lymph-spaces of the tissues may be considered as standing at a higher pressure than the blood in the venous trunks, for instance in the jugular vein. That is to say, the lymphatic vessels as a whole form a system of channels leading from a region of higher pressure, viz. the lymph-spaces of the tissues, to a region of lower pressure, viz. the interior of the jugular and subclavian veins. This difference of pressure will, as in the case of the blood vessels, cause the lymph to flow onward in a continuous stream. Further, this flow, caused by the lowness of the mean venous pressure at the subclavian vein, will be assisted at every respiratory movement, since at every inspiration the pressure in the venous trunks becomes, as we shall see in dealing with respiration, negative, and thus lymph will be sucked in from the thoracic duct, while the increase of pressure in the great veins during expiration is warded off from the duct by the valve at its opening. In the third place, the flow may be increased by rhythmical contractions of the walls of the lymphatics themselves, which, as we have seen, are remarkably muscular; and the peculiar interlacing of the muscular fibres above each valve suggests that the walls here act after the fashion of a tiny heart and by a rhythmical systole drive on the fluid, which by the action of the valve below collects at the spot. We have however no experimental proof of this; for, though rhythmic variations have been observed in the lacteals of the mesentery, it is maintained that these are simply passive, *i.e.* caused by the rhythmic peristaltic action of the intestine, each contraction of the intestine filling the lymph-channels more fully, and are not due to contractions of the walls of the lacteal vessels themselves. In some of the lower animals, for instance in the frog, the muscular walls of the vessels are developed at places into distinctly contractile propulsive-organs, spoken of as lymph-hearts, of which we shall have something to say presently. Lastly, it is at least open for us, on the strength of the analogy that osmosis may give rise to increased pressure on one side of a diffusion septum, to suppose that the very processes which give rise to the appearance of lymph in the lymph-spaces of the tissues, tend themselves to promote the flow of lymph. We have at least, under all circumstances, one or other of these causes at work, promoting a continual flow from the lymphatic roots to the great veins. They are together sufficient to drive, in man, the lymph from the lower limbs and trunk, against the effects of gravity, into the veins of the neck. In the upper limb, the influences of gravity owing to the varied movements of the limb, are as often favourable to, as opposed to, the natural flow of the lymph; but as we have already said, a long-continued unfavourable action of gravity, especially in the absence of the aid of movements in the skeletal muscles, as when the arm hangs down motionless for some time, leads to accumulation of lymph at its origin in the lymph-spaces. The strength of the causes combining to drive on the lymph is strikingly shewn in animals when the thoracic duct is ligatured; in such cases a very great distension of the lymphatic vessels below the ligature is observed.

§ **301**. Although the phenomena of disease and, perhaps, general considerations render it probable, that the nervous system governs in some way the stream of lymph, regulating it may be not only the flow along the definite lymph-canals but also the transit of plasma into the lymph-spaces and the escape of lymph thence into the definite canals, our knowledge on these points is very imperfect. We have no proof that the muscular fibres in the walls of the lymphatic vessels are governed by nerves, or that the lymph spaces are influenced directly by nervous action; and most of the attempts to demonstrate any direct action of the nervous system on the lymphatics have hitherto failed.

It is very difficult to dissociate any such direct action from an indirect influence through vaso-motor changes; for the condition of the vascular system largely affects the formation and hence the flow of lymph. Thus if, in a dog, cannulæ having been placed in the lymphatic trunks leading from each of the hind feet, the sciatic nerve on one side is divided, the flow of lymph from the foot on that side is greater than on the intact side, but is diminished on stimulation of the peripheral end of the nerve, the diminution being followed by a subsequent increase. The section of the nerve however leads to arterial dilation, the stimulation of the nerve to arterial constriction; and until other reasons be shewn, we may attribute the increased or diminished flow of lymph to an increased or diminished transudation from the fuller or emptier blood vessels. And this interpretation is supported by the fact that when stimulation of the nerve is so conducted as to lead to arterial dilation (§ 168) the result is not a diminished but an increased flow of lymph. Again if the cervical sympathetic in a rabbit be divided on one side and a solution of the blue pigment, sulphindigotate of soda, be injected into the venous system, the ear on that side becomes blue before the other, because the pigment passes more rapidly from the blood vessels into the lymph-spaces of the connective tissue and the blueness also passes away sooner because it is sooner washed away by the subsequent uncoloured lymph. But here too the increased transudation may be regarded as simply the result of the greater fulness of the blood vessels.

§ **302**. The passage of material, namely, of water containing certain substances in solution, from the interior of the blood vessel where they form part of the plasma into the lymph-capillary where they are called lymph consists of two steps: the passage from the blood vessel into the lymph space, and the passage from the lymph space into the lymph-capillary; for, as we have seen, it is only in particular places that the lymph-capillary immediately surrounds the blood vessel. Once arrived in the lymph-capillary the lymph finds an open path along the rest of the lymphatic system, but the connection between the lymph-space and the lymph-capillary is, as we have seen, peculiar and at least not a free and open one.

The passage of material from the blood vessel into the lymph-space we speak of as transudation. What can we say as to the nature of this process? There are two known physical processes with which we may compare it: diffusion through a membranous or other porous partition, and filtration through a similar partition. Diffusion, though influenced by fluid pressure, is not the direct result of fluid pressure but may on the contrary be the cause of differences of pressure on the two sides of the partition, and may work against fluid pressure. When a strong solution and a weak solution of salt are separated by a diffusion septum, diffusion takes place whether the columns of fluid be at the same level on the two sides of the septum or at different levels; and if the columns be at the same level to start with, that of the stronger solution soon comes to exceed the other in height, on account of the osmotic flow of water from the weaker into the stronger solution. Filtration on the other hand is the direct result of pressure; without difference of pressure filtration does not take place; and, the filter remaining of the same nature and in the same condition, the amount of filtrate is dependent on the amount of pressure. May we speak of the process of transudation as a simple process of diffusion or a simple process of filtration, that is to say, can all the phenomena of transudation be explained as simply the results of one or other of these physical processes? Diffusion by itself will not account for the results; for the proteids of the blood-plasma are indiffusible or very nearly so and yet the lymph contains a considerable quantity of these proteids. We have no satisfactory knowledge of the exact composition of lymph as it exists in the lymph-spaces. In the lymph of the larger lymph-trunks the diffusible saline substances are present in about the same proportion, and the indiffusible proteids to about or less than half as much as in blood-serum; and we may perhaps assume that the lymph in the lymph-spaces contains relatively less proteids but has otherwise the same composition as blood-plasma. Mere diffusion would not give rise to a fluid of such a nature. Can we speak of transudation then as a filtration? The blood is undoubtedly flowing through the capillaries and other small vessels under a certain pressure; we have seen (§ 116) that the pressure is roughly speaking about 30 mm. Hg.; and it would be possible to select such a filter or porous partition as would at about this pressure permit the passage of a certain quantity of the inorganic and crystalline constituents of blood-plasma to pass through in company with a relatively smaller quantity of the proteids and a large quantity of the water, the red and white corpuscles being excluded. Such a filtrate would be more or less of the nature of lymph; and so far we might be justified in speaking of the transudation of lymph as a process of filtration. But the transit through the living wall of the blood vessel is affected by circumstances in a manner so different from the manner in which the same circumstances affect the transit through an ordinary lifeless filter, that we gain but little, and may be led into error by speaking of the process as a filtration. Substances in solution or otherwise, pass through a filter when the pressure is sufficient to drive them through the passages furnished by the interstices existing in the substance of the filter. In the case of an ordinary filter the substance of the filter is within limits permanent, and the passages correspondingly constant. The living wall of a capillary however is not a constant unchanging thing. The epithelioid plates and other elements which constitute it are alive, and being alive are continually undergoing change and are especially subject to change; moreover, as we have seen, (§§ 22, 23) the vascular walls appear to be continually acting upon and being acted upon by the blood. Hence a change in the blood tends to cause changes in them; and these changes may materially affect in one direction or another their action as filters. In an ordinary filter increase of pressure necessarily entails increase of filtration; in a living filter it may or may not, and the same increase of pressure may according to circumstances produce very different results as regards the transudation of lymph.

Thus it seems reasonable to suppose as we have suggested (§ 227) that, other things being the same, an increase of blood-pressure should necessarily increase the transudation of lymph. Hence when a small artery dilates, since the pressure in the still smaller branches and capillaries of that artery is, as we have more than once pointed out, increased, more lymph appears in the lymph-spaces; indeed it is one of the main purposes of the widening of small arteries to supply the elements of the tissue with more lymph, that is, with more food. But it does not therefore follow that under all circumstances widening of the artery should increase the passage of lymph; something may occur to counteract the natural effect of the increased pressure in the blood vessels. An instance of this seems to be afforded by the case of the submaxillary gland, when the chorda nerve is stimulated while the gland is under the influence of atropin. As we have seen, though the arteries dilate, no secretion takes place; and we cannot explain the absence of a flow into the alveoli by supposing that the extra amount of lymph which would in normal circumstances form part of the secretion, and in the case of a fairly copious secretion would be considerable, now passes away by the lymphatics without reaching the cells of the alveoli, for in such cases no extra flow in the lymphatics leading from the gland has been observed, and there is no accumulation of lymph in the connective tissue of the gland. Apparently, for some reason or other, in spite of the increased pressure in the blood vessels more lymph than usual does not pass into the lymph-spaces.

Then again, as we shall presently have occasion to point out, an increase of pressure in the blood vessels produced by obstruction to the venous outflow is much more efficient in promoting an increase of transudation, at all events an abnormal increase, than is an increase of arterial pressure; and the difference between the two cases appears to be too great to be accounted for on the ground that an obstruction to the venous outflow raises the pressure within the capillaries and small vessels more readily and to a higher degree than does the widening of the arteries. Moreover that obstruction to venous outflow does not produce its effects in the way of transudation simply and merely by raising the capillary pressure is shewn by the fact that the same amount of obstruction may or may not give rise to excessive transudation according to the condition of the blood or other circumstances. For instance, though the obstruction produced by ligaturing a vein frequently causes excessive transudation, it does not always cause it, and the femoral vein of a dog may be ligatured without any excessive transudation taking place; yet if, after the ligature, certain changes be induced in the blood excessive transudation occurs in the leg, the vein of which has been ligatured but not elsewhere. Pointing towards the same conclusion is the fact that excessive transudation more readily occurs when a vein is plugged by a thrombus arising from abnormal conditions of the vascular system than when a vein is simply ligatured. And in general we may say, and this is a point to which we shall return, that two things chiefly determine the amount of transudation: the pressure of the blood in the blood vessels, and the condition of the vascular walls in relation to the blood, the latter being at least as important as the former.

Another aspect of the matter moreover deserves attention. In filtration the movement takes place through the filter in one direction only, whereas in the living body, the passage of material through the capillary wall takes place in two opposite directions. In all the tissues, though more perhaps in certain tissues than in others, the passage from the blood vessel into the lymph-space is accompanied by a passage from the lymph-space into the blood; while food for the tissue passes in one direction, waste products pass in the other. In a secreting gland the greater part of the lymph coming from the blood vessels, the water and other matters, pass away into the lumen of the alveolus after undergoing changes in the cell; but even in such a case there is some return from the cells into the blood vessels, carbonic acid for instance if nothing else is given up by the cells to the blood; and in such organs as a muscle or the liver, the backward stream of material from the tissue to the blood is extensive and important. Moreover this backward stream works against pressure; indeed, as may be seen in a muscle, it is when the blood vessels are dilated and the pressure in the capillaries and small vessels highest, as during and after the contraction of the muscle, that the passage from the tissue into the blood is most energetic. Many of the waste products of the tissue are it is true diffusible, and we might be tempted to say that while the lymph which feeds the tissue traverses the vascular wall by filtration in the direction of pressure the waste products return to the blood against pressure by diffusion; but such a view cannot at present be regarded as proved; and if it be true as is maintained by some, that lymph, including the proteids, may at times be re-absorbed from the tissue into the blood vessels, it is distinctly contradicted. We shall have to return to this question when we come to deal with the secretion of urine; but meanwhile we may adopt the conclusion, which is especially supported by the phenomena of disease, that while diffusion and filtration play their respective parts, diffusible substances passing in and out of the blood more readily than indiffusible substances and an increase of pressure tending to promote transudation, the condition of the vascular wall so profoundly influences the transit of material as to render the process very complex. We may probably regard it as too complex to be compared even with filtration through a filter capable of widely changing in texture from time to time, and as more nearly resembling the process of secretion.

Concerning the passage of the lymph from the confined lymph-spaces into the open gangways of the lymph-capillaries we know very little. If, as some think, the cavity of the lymph-capillary is shut off on all sides and completely by a continuous lining of sinuous epithelioid plates, then the passage from the lymph-space into it must be regarded as a sort of repetition of the passage from the blood-capillary into the lymph-space, as a second transudation. But if as others think, and as on the whole seems more probable, the lymph-spaces open, at places, directly into the lymph-capillaries the passage is a simply mechanical affair determined by the freedom of these openings.

In either case the flow from the lymph-spaces will be facilitated by all events which promote, and checked by those which hinder the flow of lymph along the lymph-capillaries and the other lymphatic channels.

We may here remark as influencing the quantity of lymph in the lymph-spaces and vessels, that the quantity of lymph taken up from the lymph-spaces by the actual elements of the tissue may vary considerably. We remarked in § 30 on the peculiar relations of living tissue to water, and there are reasons for thinking that the very substance of a cell or a fibre (a muscular fibre for instance) may hold in itself a larger quantity of water at one time than at another. The water thus taken up or given out, and the substances which may be carried in solution by that water, come from and go to the lymph. The condition of the tissue determines by itself the amount of lymph in the lymph-spaces.

§ **303**. Under the influence of all these several actions the lymph in the various lymph-spaces of the body varies in amount from time to time, but under normal circumstances never exceeds certain limits. Under pathological conditions those limits may be exceeded, and the result is known as *oedema* or dropsy. Similar excessive accumulations of lymph may occur not in the ordinary lymph-spaces, but in those larger lymph-spaces, the serous cavities, any large excess of fluid in the peritoneal cavity being known as *ascites.*

The possible causes of œdema are on the one hand an obstruction to the flow of lymph from the lymph-spaces, and on the other hand an excessive transudation, the lymph gathering in the lymph-spaces faster than it can be carried away by a normal flow; with the former the lymphatic system itself, with the latter chiefly the vascular system is concerned. As a matter of fact however œdema is almost always, if not always, due to abnormal conditions of the vascular system, and is the result not of hindered outflow but of excessive transudation.

Owing to the numerous anastomoses of the lymph-vessels and the consequent establishment of collateral streams, obstruction in the lymph-passages themselves rarely if ever gives rise to œdema; and it may be here remarked that owing to the same free collateral communication between the lymph-vessels the labyrinthine passages of the lymphatic-glands do not offer the serious obstacle to the onward flow of the general lymph-stream as might at first sight be supposed. Nor have we at present any knowledge which would lead us to suppose that any physiological changes in the walls of the lymphatic-vessels or of the lymph-capillaries, or in the lymph-spaces, by giving rise in some way to obstacles to the flow of lymph, ever lead to an accumulation of lymph in the latter.

One kind of œdema we have already touched upon in speaking of the capillary circulation (§ 183), viz. the "inflammatory" œdema. In this kind of œdema owing to changes in the vascular walls a larger amount of transudation passes into the lymph-spaces, and that transudation is richer in proteid matters, and contains a larger amount of the fibrin factors or at all events is much more distinctly coagulable than ordinary lymph, as well as crowded with migrating corpuscles. Allied to this inflammatory œdema is the increase of lymph, also apparently changed somewhat in character, which appears as "effusion" in the serous cavities when these are inflamed, as in pleurisy and peritonitis.

One of the most common forms of œdema is an œdema of primarily, though not wholly, mechanical origin, œdema arising from obstruction to the venous flow; under these circumstances more lymph passes into the lymph-spaces than the lymph-vessels are able to carry away. If the femoral vein be tied the leg may become œdematous, and, as we have said, œdema is a common result of the plugging or obstruction of veins through disease; the œdema which is so common an accompaniment of heart-disease involving obstruction to the return of venous blood to the right side of the heart, and the ascites which follows upon hindrance to the portal flow are instances of œdema of this kind. We have already remarked on the relation of transudation to blood-pressure; and in venous obstruction the rise of pressure within the small blood vessels is distinguished from that due to arterial dilation by being accompanied with a want of adequate renewal of the blood; this probably affects the epithelioid lining of the blood vessels in such a way as to increase the transudation. And indeed, as is seen in cases of heart disease with prolonged or repeated venous obstruction, the œdema as time goes on and the tissues become impaired is more easily excited and with greater difficulty removed, though the actual amount of obstruction, the actual increase of pressure in the small vessels, remains the same, or at least is not proportionally increased.

Still another kind of œdema is one due to changes taking place in the blood, quite apart from variations of blood-pressure. This kind of œdema is seen in some diseases of the kidney, in "Bright's disease" for instance. In such cases the blood contains less proteids, and indeed less solids, is more watery and of lower specific gravity than is normal. But the œdema is not in these cases to be explained on the view that the more watery blood passes more readily through the capillary walls, for it may be shewn experimentally that the mere thinning of the blood, as by the injection of normal saline solution into the blood vessels, will not at once lead to œdema, at least in the limbs and trunk, and it is these which in Bright's disease especially become œdematous. In all probability the œdema of Bright's disease if it be really due to the abnormal character of the blood, is produced by the abnormal blood so acting on the blood vessels that these allow a transudation greater than the normal.

But these are pathological questions into which we must not enter here. We have touched upon them because they illustrate the important processes taking place in the lymph-spaces, and as we have more than once insisted the lymph in the lymph-spaces is the middleman of all the tissues, and hence facts illustrating the laws which govern the flow of lymph into and out of the lymph-spaces are of fundamental physiological importance.

§ **304**. *Lymph-hearts.* In the frog and other amphibia and in reptiles the flow of lymph into the venous system is assisted by rhythmically pulsating muscular lymph-hearts, which present many curious analogies with the blood-heart. The frog possesses four lymph-hearts. Of these two, belonging to the hind limbs, are placed one on each side of the coccyx, near its end, and, being covered only by aponeurosis and the skin, may, without dissection, be seen beating. Two anterior ones are placed on the transverse processes of the third vertebræ, and are covered from view by the shoulder girdle. Each lymph-heart is a more or less oval sac lying in one of those lymph sacs or cavities lined with sinuous epithelioid plates, which as we have said are present in the frog. It is continued at one end, by an orifice guarded with valves, into a small vein which opens, in the case of the posterior heart, into a crural vein, and in the case of the anterior hearts, into a jugular vein. The wall consists of muscular fibres arranged in a plexiform manner, and supported by a considerable amount of connective tissue. These fibres are striated and branched, and are intermediate in character between cardiac and skeletal muscular fibres. Nerve fibres terminate in these muscular fibres, and the muscular wall, unlike that of the blood-heart, is supplied with capillary blood vessels. The interior is lined with epithelioid plates of sinuous outline, and this lymphatic lining is continued along a number of openings or pores, by which the cavity of the heart opens into the surrounding lymph-space. When the heart contracts the contents are driven into the vein, the lymphatic pores being closed by the approximation of the contracting muscular fibres; when the heart dilates, the fluid in the vein is prevented from returning by the valves at its mouth, while the lymph enters readily from the surrounding space through the now open pores. In the frog regular lymphatic vessels are scanty; hence these lymph-hearts become of considerable importance in promoting the flow of lymph. The lymph-hearts of reptilia are similar in structure and function. In the frog, in which they have been chiefly studied, the action of the lymph-hearts is in a measure dependent on the spinal cord. The posterior lymph-hearts belonging to the hind limbs are connected by means of the delicate tenth pair of spinal nerves with a region of the cord opposite the sixth or seventh vertebra, in such a way that section of the nerve or destruction of the particular region of the cord suspends or destroys their activity. The anterior pair are similarly connected with a region of the spinal cord opposite the third vertebra. Each pair therefore seems to have a 'centre' in the spinal cord; but it is probable, though observers are not wholly agreed, that the hearts, after destruction of their spinal centre, ultimately resume their rhythmic beats, so that the dependence of their activity on the spinal centre is not an absolute one. Like the heart of the blood-system, the lymph-hearts may be inhibited, and that in a reflex manner, the inhibition centre being moreover in the medulla oblongata. If a frog be carefully observed, the activity of the lymph-hearts will be found to vary largely, and these variations appear to be in part due to nervous influences; so that in this way the movement of lymph, and hence the processes of absorption, are in this animal directly dependent on the nervous system.

SEC. 11. ABSORPTION FROM THE ALIMENTARY CANAL.

§ **305**. We may now return to consider the absorption of the products of digestion, that is to say, the passage of these bodies from the interior of the alimentary canal, where they are really outside the body proper, into the body itself. For simplicity's sake we may consider digestion in a broad way as the conversion of practically non-diffusible proteids and starch into more diffusible peptone and highly diffusible sugar, and as the emulsifying, or division into minute particles, of fats. We have seen reason to believe that some of the sugar may be changed into lactic acid or even into butyric or other acids, that some of the proteids are carried beyond the peptone condition into leucin and other bodies, and that some of the fat may be saponified; and it may be that some of the proteid material of the food passes into the body as albumose or even as parapeptone, or in some other little changed condition. But we may probably with safety, for present purposes, assume that the greater part of the proteid is absorbed as peptone, that carbohydrates are mainly absorbed as sugar, and that the greater part of the fat passes into the body as emulsified but otherwise unchanged neutral fat; and we may neglect the other conditions of digested food as subsidiary, and as far as absorption is concerned, unimportant.

We have seen that two paths are open for these products of digestion, one by the capillaries of the portal system, the other by the lacteals. It cannot be a matter of indifference which course is taken. For if the products pass by the lacteals they fall into the general blood-current after having undergone only such changes as they may experience in the lymphatic system; while if they pass into the portal vein they are subjected to certain powerful influences of the liver (which we shall study in a future chapter) before they find their way to the right side of the heart. We may therefore consider first which of the two paths is, as a matter of fact, taken by the several products, and subsequently study the mechanism of absorption in the two cases.

The Course taken by the Several Products of Digestion.

§ 306. From what has already been said we have been led to regard the villi as the most active organs of absorption, and the structure of a villus leads us further to conclude that the diffusible peptones and sugar pass, together with the water in which they are dissolved, into the superficially placed capillary network of the villus and so into the portal system, while the merely emulsified fat, unable to traverse the wall of the capillary, passes on to the deep-seated lacteal radicle, and so finds its way into the lymphatic system. And the results of observation and experiment, as far as they go, support this view.

Fats. After a meal containing fat the lymph of the lacteals contains fat, and is now called chyle; and the richer the meal in fat the more conspicuous is the fat in the lymph-vessels. We cannot however prove that all the fat of a meal absorbed from the alimentary is poured by the thoracic duct into the venous system. If a meal containing a known quantity of fat be given to a dog and the small quantity of fat present in the fæces corresponding to the meal be subtracted from that amount, we can determine the amount of fat absorbed, for we have no evidence whatever that any appreciable amount of fat undergoes a destructive decomposition in the alimentary canal. Collecting by means of a cannula inserted into the thoracic duct the whole of the chyle during and after the meal so long as it remains milky, shewing that fat is being absorbed, we can ascertain the quantity of absorbed fat, which would, but for the operation, have passed into the venous system. When this has been done, a very remarkable deficit, amounting it may be to 40 or 50 p.c. has been observed; that is to say, of every 100 parts of fat which disappear from the alimentary canal only about 60 parts find their way through the thoracic duct into the venous system.

Are we then to conclude that the missing quantity finds its way into the portal system? Now the portal blood does, during digestion, contain a certain quantity of fat; indeed the serum is said at times to appear milky from the presence of fat. But the whole circulating blood during the digestion of a fatty meal contains, for a while, the fat poured into it by the thoracic duct; and it has been ascertained in the dog that the blood of the portal vein during digestion contains not more but less fat than the blood of the carotid artery, so that the fat which appears in the portal blood during digestion is, for the most part at least, not fat absorbed by the capillaries of the alimentary canal but fat absorbed by the lacteals. Moreover, when the chyle of the thoracic duct is diverted through a cannula, and not allowed to flow into the blood, the quantity of fat in the portal blood as in the blood at large is very small indeed. Lastly, when a villus of an intestine in full digestion of fat is treated with osmic acid, fat cannot be recognized by the microscope within the capillaries or other blood vessels, though it abounds outside them in the substance of the villus and in the lacteal radicle.

We may probably therefore infer with safety that all or at least very nearly all the fat absorbed from the intestine takes the path of the lacteals. As to the deficit mentioned above, that is as yet without explanation. It may be that in some way, on its course, in the lymphatic glands, for instance, the fat is taken away from the chyle, hidden so to speak somewhere away from both chyle and blood; but on this point we have no exact information.

§ **307**. *Water and Salts.* If, in an animal, the rate of flow of lymph or chyle through a cannula placed in the thoracic duct be watched, and water or, to avoid the injurious effect of simple water on the mucous membrane, normal saline solution be then injected in not too great quantity into the intestine, no marked increase in the flow of chyle through the cannula is observed. From this we may infer that the water of the intestinal contents is absorbed not into the lacteals but into the portal system. If however a very large quantity of the normal saline solution be injected so as to distend the intestine, then the flow of chyle is increased to some extent. It would appear therefore that while under normal conditions the water passes from the intestine mainly into the portal blood, some of it may under circumstances pass into the lacteals.

With regard to the course taken by ordinary saline matters we possess no detailed information. When special salts such as potassium iodide and others, easily recognized by appropriate tests, are introduced into the intestine, they may be speedily detected both in the blood and in the contents of the thoracic duct; but whether, in such cases, these salts find their way into the thoracic duct by the lacteal radicle of the villi, or pass into the lymph stream at some later part of its course, we do not know. Nor can we with regard to such a salt as sodium chloride, state absolutely that it passes mainly with the water into the portal blood, though we may fairly suppose this to be the case.

§ **308**. *Sugar.* Both blood and chyle contain, normally, a certain small amount of sugar; and careful inquiries shew that the percentage of sugar in chyle and in general blood is fairly constant, neither being to any marked extent increased by even amylaceous meals; on the other hand, a meal containing sugar or starch does temporarily increase the quantity of sugar in the portal blood. From this we may infer that such portions of the sugar of the intestinal contents as are absorbed as sugar pass exclusively by the portal vein. We may however here call attention to the difficulties attending an argument of this kind. In the first place the quantitative determination of a small amount of sugar in so complex a fluid as blood is attended with great difficulties and uncertainties. In the second place a very large quantity of blood is at any one moment streaming through the capillaries of the alimentary canal; and we may perhaps speak of the quantity which passes through them during the whole period of digestion as being enormous. Hence though each 100 cc. in passing through the capillaries might take up a quantity of sugar so small as to fall almost within the limits of errors of observation, yet the whole quantity absorbed during the hours of digestion might be considerable; or to put it in another way, an error of observation, unavoidable with our present means of analysis, on a sample of blood taken from the portal vessels might lead to a wholly unwarranted conclusion that sugar was or was not being absorbed. Making every allowance however for these difficulties, the increase of sugar which has been observed in the portal blood during digestion seems too great to permit of any other conclusion than that sugar is really absorbed from the alimentary canal by the blood vessels.

When however a large quantity of sugar dissolved in a large quantity of water is present in the intestine, the sugar in the chyle is said to be increased. In such a case the excess of water, as stated above, passes into the lacteals, and in so doing appears to carry some of the sugar with it.

§ **309**. *Proteids.* The difficulties attending the experimental determination of the path taken by proteids are greater even than in the case of sugar; for the exact quantitative estimation of peptone in blood (and we are assuming that proteids are mainly absorbed as peptone) is a task of the greatest difficulty, one compared with which that of estimating sugar appears almost easy. Bearing this in mind we may state that all observers are agreed that peptone is absent from chyle or at least that its presence cannot be satisfactorily proved. On the other hand, while some observers have succeeded in finding peptone in the portal blood after food, but not during fasting, many have failed to demonstrate the presence of peptone in the blood either of the portal vein or of the vessels at large even after a meal containing large quantities of proteids. Of course, as we argued in speaking of the absorption of sugar, the quantity of peptone passing into the portal blood at any moment might be small, and yet a considerable quantity might so pass during the hours of digestion. We may suppose moreover that that which does pass is immediately converted, possibly by some ferment action, into one or other of the natural proteids of the blood, or otherwise disposed of; and indeed peptone injected carefully and slowly into a vein disappears from the blood, though little or even none passes out by the kidney. And the view that peptone is so changed, possibly in the very act of absorption, is supported not only by the statement that peptone may be found in the practically bloodless wall, that is, mucous membrane, of the intestine removed from a dead animal even when it appears to be absent from the blood, but also and especially by the following observation. If an artificial circulation of blood be kept up in the mesenteric arteries supplying a loop of intestine removed from the body, the loop may be kept alive for some considerable time. During this survival a considerable quantity of peptone placed in the cavity of the loop will disappear, *i.e.* will be absorbed, but cannot be recovered from the blood which is being used for the artificial circulation, and which escapes from the veins after traversing the intestinal capillaries. The disappearance is not due to any action of the blood itself, for peptone introduced into the blood before it is driven through the mesenteric arteries in the experiment may be recovered from the blood as it escapes from the mesenteric veins. It would seem as if the peptone were changed before it actually gets from the interior of the intestine into the interior of the capillaries.

But the argument that the absence of peptone from the blood is no proof that peptone is not absorbed into the blood may also be applied to the chyle, and thus leaves us unable to draw a conclusion as to the path of the proteids. The following indirect proof that peptone does not pass into the chyle has been offered, but it too is open to objection. We shall see hereafter that the absorption of proteid material leads to an increase in the elimination of urea by the kidneys. So marked is this increase, that unless there be clearly some other causes at work leading to an increase of urea, such as fever for instance, an increase of urea in the urine following upon the administration of proteid food may be taken as a proof that the proteid food has been digested and absorbed. Now if in a dog the thoracic duct be successfully ligatured so that the chyle cannot pass as usual into the blood, and the dog be fed on proteid food, as free as possible from fat, so as not unnecessarily to load the obstructed lacteals, an increase in the urea of the urine is observed as usual. Obviously in such a case the proteid food is absorbed, and obviously also does not pass into the blood through the thoracic duct (the success of the ligature having been proved by post mortem examination). But the experiment, though as far as it goes supporting, does not rigorously prove the view that the proteids are absorbed by the capillaries of the alimentary canal; for the thoracic duct and lymphatics below the ligature were found largely distended, and lymph and chyle appear to have escaped from the vessels; hence it is possible that some at least of the proteids were absorbed by the lacteals of the intestine, but finding their usual path blocked made their way into the blood stream.

We may therefore say that the results of experiment while they do not definitely prove, give some support to, and at least do not contradict, the view which we a little while ago put forward as probable, namely that the proteids, transformed into diffusible peptones, pass into the blood vessels and not into the lacteals.

But, if this view be provisionally accepted, it must be on the understanding that it is probable only; and it may be that proteids do not take the same paths and are not absorbed in the same condition in all animals. The experiments just related were performed on dogs, that is to say on carnivorous animals whose (natural) food contains a considerable quantity of fat, and whose lacteals might therefore be considered as preoccupied in the absorption of fat. The food of herbivora on the other hand contains a relatively small amount of fat; and if in these animals all the proteids and carbohydrates are absorbed by the blood vessels, there is comparatively little left for the lacteals to do. Yet in these animals the lacteals and the lymphatics are well developed. In the villus of a herbivorous guinea-pig or rabbit, though the reticular tissue is very scanty as compared with that present in the villus of a dog, the lacteal chamber is, relatively to the diameter of the villus, not merely as large as but much larger than in the dog. It is difficult to suppose that this wide chamber is intended solely for the absorption of the relatively small amount of fat present in vegetable food. The question which we are discussing is clearly at present to be regarded as by no means settled.

The Mechanism of Absorption.

§ **310**. *The Absorption of Fats.* We have now to consider the manner in which these several substances pass into either the lacteal radicle or the capillary blood vessel. It will be convenient to begin with the absorption of the fats.

We have seen reason § 280 to think that the fats, remaining chiefly as neutral fats, are emulsified in the intestine, by means of the bile and pancreatic juice, the small quantity of soap which is formed probably serving simply the purpose of facilitating the emulsification.

The neutral fats so emulsified pass in the first instance into the bodies of the columnar cells of the villi. It has, it is true, been maintained by some that they pass *between* the cells and not into them; but the evidence is distinctly against this view. The cells may again and again be seen crowded with fat, and the cases in which the fat has been seen between the cells and not in them are due to the extrusion of the fat, during the shrinking of the villus in the course of preparation, from the cells into spaces between the cells. In the frog, in which there are no villi, and in which the folds of mucous membrane serving the purposes of villi do not so readily shrink, the presence of fat globules in the cells after a fatty meal can always be easily demonstrated by osmic acid preparations. Since no such collections of fat globules are seen in the cubical cells of the glands of Lieberkühn we infer that these have nothing to do with the absorption of fat.

How the fat enters into the substance of the cell we do not know. We may presume that the striated border plays some part, but what part we do not know. Though, as we have seen, the rods making up the border appear able to move, to change their form, we have no evidence that the fat is introduced into the cells by means of any movements of these rods. We may imagine that the globules pass into the cell substance by help in some way of these rods, through amœboid movements comparable with the ingestive movements of the body of an amœba; but we have no positive evidence to support this view. We said (§ 247) that bile promotes the passage of fat through membranes, possibly by in some way promoting a closer contact between the particles of fat and the substance of the membrane; but even if bile has this effect on the surface of the cells, its action in this respect can be subsidiary only.

Within the columnar cell the fat may be seen, both in osmic acid preparations, and in fresh living cells, to be disposed in globules of various sizes, some large and some small, each globule placed in a space of the protoplasmic cell substance. It does not follow that the fat actually entered the cell exactly in the form of these globules; it may be that the fat passes the striated border in very minute spherules which, reaching the body of the cell, run together into larger globules; but whether this is so or not we do not know.

From the columnar cell the fat passes into the spaces of the reticular tissue of the villus. It has, it is true, been contended that it passes along the substance of the bars of the reticulum; but in carefully prepared osmic acid specimens of a villus in active digestion of fatty food, the fat may be distinctly recognized as largely filling up, still in the form of globules of various sizes, the spaces in the meshes of the reticulum which are not occupied by the leucocytes or allied wandering cells. We have seen (§ 260) that the bases of the columnar cells, through the gaps in the basement membrane, directly abut upon the labyrinth of spaces; and the fat once out of the base of the cell is free in the spaces of this labyrinth. How it issues from the cell we do not exactly know: possibly by a process analogous to the excretion of solid matters by an amœba.

From the labyrinth of spaces of the reticulum of the villus the fat passes into the cavity of the lacteal radicle; and it is worthy of note that in the passage it undergoes a change. In the interior of the intestine, in the substance of the columnar cell, and apparently in the labyrinth of the reticulum it is simply emulsified fat consisting of globules small and large; within the lacteal radicle it consists partly of the same easily recognized globules but partly of the extremely divided 'molecular basis' (§ 299); it is now no longer emulsified fat but chyle. How and by what means this extremely minute division of the globular fat into the 'molecular basis' takes place we do not know; nor do we know the exact manner in which the fat passes from the spaces of the reticulum into the interior of the radicle. If the sheet of sinuous epithelioid plates which forms the sole wall of the chamber is discontinuous, presenting here and there gaps between the plates, the passage presents no difficulty in itself, but does raise the difficulty why there is so great a difference between the chyle inside the chamber and the fat outside. On the other hand, if as observations seem to shew the lining in question is actually continuous, the fat must pass into the lacteal radicle either through the substance of the plates or through the junction lines of cement. Such a passage presents difficulties; but at the same time we can conceive that in the struggles of such a passage some of the fat might be converted into the molecular basis.

We may here perhaps remark that the contents of the lacteal radicle consist not exclusively of fat, but of fat accompanied by the proteid and other substances which go to make up the chyle. Proteid and other substances besides fat are also present in the lymph which occupies in part the labyrinth of the body of the villus, and are derived, like the lymph elsewhere, from the blood of adjacent capillaries; at least, they are in part so derived, though it may be not wholly, for as we have just seen the passage of proteid material from the intestine into the substance of the villus past the capillaries though not proved, must still be considered as possible.

We have seen (§ 262) that the spaces of the reticulum of the villus are more or less occupied by wandering cells of which we spoke under the general term of leucocytes. These do not all present the same appearances and most probably are not all of the same kind. A number of them may be distinguished by the fact that the cell body is loaded with discrete granules which stain readily and deeply with certain anilin dyes, and which though not of a fatty nature turn black with osmic acid.

Some of these leucocytes wander not only through the labyrinth of the reticulum but pass into the epithelium between the cells, and may project processes into, or even make their way eventually into the interior of the intestine; or following the reverse course may wander from between the epithelium cells into the body of the villus; some of them moreover undoubtedly contain fat. Hence the view has been suggested that these leucocytes are important agents, indeed the chief agents in the absorption of fat. It has been supposed that they, receiving the globules of fat into their cell substance, in fact eating the fat exactly after the manner of an amœba, either while projecting between the columnar cells, in which case they carry their burden of fat through the epithelium into the villus, or while wandering in the labyrinth of the villus, bear it away bodily into the lymphatic system. But the number of leucocytes really containing any appreciable quantity of fat is too small to account for the amount of fat absorbed; since as we just pointed out in a certain kind of these cells, and this kind is often very abundant, the granules in the cell substance which stain with osmic acid are not fat. Nor is the abundance of leucocytes in the mucous membrane during the period of digestion a sure proof that they are concerned in absorption, but rather an indication only that active changes of some kind are going on, since after the administration of a saline such as magnesium sulphate, which produces effects the very reverse of absorption, these leucocytes are present in unusual numbers. Moreover under some circumstances, as in the villi of a new-born puppy after a meal of milk, they are absent even when digestion of fat is rapidly going on and the lacteals are filling with fat. In fact, what we stated above concerning the presence of fat in the bodies of the columnar cells shews that leucocytes can have little to do in transferring fat from the interior of the intestine into the body of villus; and there are no adequate reasons for attributing to them any real share in the transference of fat from the body of the villus into the lacteal chamber.

§ **311**. The lacteal chamber opens at the base of the villus into the valved lymphatic vessels lying below, and in these the flow of lymph (chyle) is being promoted by the various causes detailed in § 300. The pressure for instance exerted by the peristaltic contractions of the intestine helps to empty the lymphatic vessel into which a lacteal chamber opens and so promotes the emptying of the latter. In addition to this the plain muscular fibres of the villus supply a special muscular pump for the emptying and filling of the lacteal chamber. These fibres and small bundles of fibres though running in various directions (§ 262) and varying in number and arrangement in different animals, take on the whole a longitudinal direction parallel to the long axis of the villus. It has been supposed that in contracting and shortening the villus they compress the lacteal and thus empty it, and that when they relax and the villus elongates again, the emptied chamber fills once more. But a different interpretation of their action has been offered somewhat as follows. When the muscular fibres contract they shorten the villus. In thus becoming shorter the body of the villus becomes proportionately broader, since probably no great change of bulk in the reticulum takes place; in this broadening the part to give way will be the lacteal chamber, which thus becomes broader and larger. When the muscular fibres relax, the reticulum, the bars of which have been put on the stretch in a lateral direction, by elastic reaction brings back the villus to its former length, and the lacteal chamber elongates and narrows. On this view the muscular contraction expands and so fills, while the relaxation narrows and so empties the lacteal chamber. Whichever view we adopt, we may at least conclude that contractions and relaxations of the muscular fibres in some way or other alternately fill and empty the lacteal chamber, and in all probability, at all events during digestion, rhythmical contractions of these fibres are continually going on. When the villus is shortened by the contraction of the muscular fibres, the columnar cells are compressed, becoming longer and narrower; when the muscular fibres relax and the villus elongates, the columnar cells return to their previous form. The alternating changes of form to which the columnar cells are thus subjected, and the alternating changes of pressure taking place in the reticulum, may also serve to promote the passage of material through the one and through the other.

§ **312**. *The Absorption of Diffusible Substances and of Water.* On the provisional assumption which we have made that the proteids are converted into peptone, we may consider, for the present at all events, peptone, sugar and soluble salts as together forming a class distinguished from fats by their being diffusible, some more so than others. And we have made the further provisional assumption that these pass into the blood vessels and not into the lacteals.

The network of capillary blood vessels is spread as we have seen (§ 262) immediately beneath the basement membrane, and all the material which enters the lacteal chamber has to run the gauntlet of the meshes of this network. During digestion the capillaries of the intestine are filled and distended, so that at a time when absorption is taking place these meshes between the capillaries are unusually narrow. From the interior of these capillaries, here as elsewhere, transudation is taking place; these capillaries supply the lymph which helps to fill up the labyrinth of the reticulum and the lacteal chamber. But to a much greater extent than elsewhere (cf. § 302) this current of transudation from within the capillary to without is accompanied by a reverse current from without to within. The diffusible substances in question pass from the intestine through the layer of epithelium cells, through the attenuated reticular lymph-space between the basement membrane and the capillary wall, and through the capillary wall into the blood current. Their passage consists of two stages; that through the epithelium cells from the intestine to the lymph-space, and that from the lymph-space into the blood vessels. These two stages may be expected to differ, seeing that the structures concerned are different; but we may at first consider them as one, and speak of the passage from the intestine into the blood as a single event.

In speaking of these substances as diffusible we are using the term in reference to the well-known passage of such substances through thin membranes or porous partitions. When a strong solution of sugar or of common salt is separated by a thin membrane (vegetable parchment, dead urinary bladder, dead intestine, &c.) from a weak solution of sugar or of salt, the sugar or salt passes with a certain rapidity from the stronger to the weaker solution, and water passes from the weaker solution to the stronger; if, to begin with, simple water be substituted for the weaker solution the effect is at first still more striking. Peptone passes in the same manner but as we have seen much more slowly. The process is spoken of as a physical one since it is not accompanied, necessarily, by any chemical change in the diffusing substance, nor is there any necessary change in the membrane or partition. The rate at which a substance diffuses, and the total amount of diffusion which can take place, are determined by certain qualities of the substance (which we may call physical though they depend on the chemical nature of the substance) in relation to certain qualities of the membrane; thus two salts may diffuse through the same membrane at different rates, with different rates in the associated current of water, the osmotic current as it is called, from the weaker to the stronger solution; and the same substance may pass at different rates through different membranes. By a number of observations, in which various substances in solution and several known membranes or partitions have been employed, a certain number of "laws of diffusion" have been established.

Now if by the statement that diffusible substances pass by diffusion into the blood-capillaries of the intestine we are led to expect that the passage takes place exactly according to the laws established by observations on ordinary membranes we should be led into error; for the disappearance of these substances from the interior of the intestine does not take place according to the laws which regulate their disappearance from one side of an ordinary diffusion septum. This can be ascertained by introducing solutions of the substances, of various strength, into a loop of intestine, isolated in the living animal by the method described in § 250, and watching their disappearance by analysis of the contents of the loop. No very large number of experiments have been made in this way, but such as have been made all shew the difference on which we are dwelling. For instance, sodium sulphate passes through an ordinary diffusion septum with a rapidity rather greater than that of dextrose, whereas dextrose disappears from the intestine distinctly more rapidly than sodium sulphate; peptone which diffuses very slowly indeed through an ordinary diffusion septum disappears rapidly (though not so rapidly as dextrose) from the intestine; and when the details of the disappearance from the intestine of weak solutions of two salts which diffuse through an ordinary membrane at different rates, which have as it is said different osmotic equivalents, are studied, these details are quite different from those of ordinary diffusion. The more the matter is studied the more decidedly apparent becomes the difference between ordinary diffusion and the absorption of diffusible substances from the intestine.

Moreover, in such experiments on an isolated loop of intestine, the disappearance of material from the intestine is accompanied by the appearance of material in the intestine, namely proteid and other substances; these are derived from the blood. And the question arises, If we allow ourselves to regard the passage of material from the interior of the intestine into the blood as carried out by ordinary diffusion, why we should not regard the passage of material from the blood into the interior of the intestine as being also carried out by means of diffusion? But such a passage we speak of elsewhere as a "secretion"; and everything which we have hitherto learnt has led us to the conclusion that secretion is a different and much more complex thing from mere diffusion. Even admitting that the succus entericus is of subordinate importance in carrying out digestive changes, we cannot doubt that the glands of Lieberkühn secrete, and may with some reason suppose that the columnar cells of the villi do so also. Hence even if we assume the existence of an ordinary diffusion current from the blood into the intestine, accompanying and complementary to an ordinary diffusion current from the intestine into the blood, we are compelled to admit that with this there coexists, at times at all events, and in varying intensity, a current of a different and more complex nature, a current which is the result of secretory activity. And results which at first sight seem explicable by the former, may, after all, be due to the latter. Thus the flow of water into the intestine with the subsequent production of a watery stool, which follows upon the introduction into the alimentary canal of a concentrated solution of magnesium or sodium sulphate, may at first sight seem to be simply the osmotic current passing from the weaker solution of the salt, namely the blood, to the stronger solution of the salt, namely the intestinal contents. But the difference between these effects of a dose of magnesium sulphate and those of a corresponding dose of sodium chloride are much greater than can be accounted for by the diffusion phenomena, by the differing osmotic equivalents of the two substances; and the more the matter is studied the more reason have we to believe that the flow of water produced by the former is to a large extent the result of suddenly increased secretory activity. So also the fact that the contents of the small intestine throughout its length retain the same amount of water relatively to the solids, that is to say maintain the same or nearly the same fluidity, whereas in the large intestine the water relatively diminishes until at last the fæces become firm and even dry, cannot be wholly explained without calling into our aid variations in active secretion as distinguished from mere physical diffusion. And in the case of a purgative such as croton oil producing a watery stool, when only a minimal, we might almost say an infinitesimal amount of its own substance can at any one time be present in the intestinal walls, the result is obviously due to active secretion.

If, however, we are thus driven to the conclusion that the passage from the blood into the intestine is a manifestation of secretory activity in which epithelium cells play a part, gradually becoming little by little more intelligible to us, why should we not admit that the passage from the intestine to the blood, which as we have seen does not accord in its phenomena with known processes of ordinary diffusion, is also brought about by the activity of cells, is in fact a kind of inverted secretion, and hence like ordinary secretion presents problems which cannot be solved by any off-hand references to known physical processes? Indeed this is the conclusion towards which observation and experiment seem to be steadily leading us. Were the alveolus of a salivary gland habitually filled with a fluid of mixed and varied nature like the contents of the alimentary canal, we should probably in our study of the gland find ourselves compelled to speak of a double current as existing in the gland, of a current from the cells to the lumen of the alveolus, and of a current from the lumen to the cells. And all along the intestine both the columnar and cubical cells, which everywhere bear the marks of being "active" cells, may perhaps be regarded as engaged in a like double function. Over the villi the receptive function, in the glands of Lieberkühn the ejective function is predominant; but as we have suggested, § 265, in the glands reception probably is not wholly absent, and we may imagine that in the villi some amount of ejection (quite apart from the action of the goblet cells) may take place.

If this view be accepted, if we admit that the entrance of digested food does not take place by ordinary diffusion, the question may be asked why are the digestive changes directed towards increased diffusibility, why are proteids converted into diffusible peptones, and why is starch converted into sugar? Because though the cell is not an apparatus for diffusion, diffusion is an instrument of which the cell makes use. When we say that peptone does not enter the blood by ordinary diffusion we do not mean that diffusion has nothing to do with the matter. The activity of a living cell is an activity, built up upon and making use of various chemical and physical processes; in it the processes of ordinary diffusion play their part as do the processes of ordinary chemical decomposition; but the cell uses and modifies them for its own ends. If as we have every reason to believe the cell of a villus passes the sugar unchanged from the intestine into the blood capillary, it makes use of diffusion to effect that passage; and if it does change the proteid into something else before it passes it on, it receives it into itself in the first instance by help of diffusion. When we say that substances do not enter the blood by ordinary diffusion we mean that the diffusion which takes place in a living cell is something so different in the results from ordinary diffusion through a dead membrane that it is undesirable to speak of it by the same name. In ordinary diffusion the results depend on the relation of the molecules of the diffusing substance to the minute pores or canals or spaces in the diffusion septum. These canals or spaces are constant in an ordinary septum; but a film of a living cell may be conceived of as a diffusion septum the pores of which are continually varying, and moreover as closing up or opening out at the touch of this or that substance; hence the passage of material through the pores of a living cell takes place according to laws quite different from those of ordinary diffusion.

§ **313**. The whole act of the absorption of substances with which we are dealing consists, as we have said, of two parts: the passage from the interior of the intestine through the epithelium cell into the lymph-spaces or reticulum of the villus, and the passage thence through the capillary wall into the blood-stream. In the experiments referred to above it has not been possible to distinguish between these two stages of the whole process; in each case we have had to make use of the terms 'from the interior of the intestine into the blood' and 'from the blood into the interior of the intestine.' Nevertheless the remarks which have just been made may be taken as referring more especially to the first stage. They lead us to the conclusion that both fats and diffusible subtances, though in different ways, are carried into the interior of the villus by the activity of the epithelium cells.

In respect to the second stage of the absorption of diffusible substances, it might be expected that part of one or other of these substances, part of the sugar for instance, arrived inside the basement membrane should slip by the capillary blood vessel and passing through the meshes of the capillary network make its way into the lacteal. And indeed, as we have seen, § 308, under certain circumstances some amount of sugar appears to take this course. But, as we have also seen, under ordinary circumstances the current, whatever be its exact nature, from the narrow lymph-spaces lying between the epithelium and the capillary into the blood-stream is strong enough to carry all or nearly all the sugar into the blood. In the establishment of this current, in this second stage of absorption diffusion always plays a part, and probably a still more conspicuous and decided part than in the first stage, seeing that the epithelioid plate of the capillary wall is a far less active structure than the columnar cell of a villus. Indeed it might be open for us to contend that this second stage was merely a matter of diffusion, whatever might be the nature of the first stage. But remembering what was said above, § 302, in discussing the transudation of lymph, it seems more in accordance with what we already know, to conclude that in this second stage also diffusion is the servant and not the master of the living capillary wall.

A word may be added concerning the special case of the peptones. As we have said, the peptones in being absorbed appear to undergo a change somewhere in the mucous membrane. We do not know exactly where or how the change takes place. It seems probable that so marked and difficult a change should require the intervention of some active living tissue, and we may therefore suppose that it is effected by the epithelium cells; but we have no exact knowledge on this point. If the change be thus carried out by means of the epithelium cells, then the latter stage of the absorption of proteids, namely the passage from the epithelium into the interior of the capillary is not a passage of diffusible peptone, but of some other non-diffusible kind of proteid. It may be however that the change takes place during the very passage of the material through the capillary wall.

The view that leucocytes are the agents of the absorption of fat, by bodily taking up the fat into their cell-substance, has by some been extended to proteids; it has been urged that these take up proteids either as peptones or in some other form and so carry them into the lymphatic system. But the evidence for this view is even less convincing than in the case of fat.

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CHAPTER II.

RESPIRATION.

SEC. 1. THE STRUCTURE OF THE LUNGS AND BRONCHIAL PASSAGES.

§ **314**. ONE particular item of the body's income, viz. oxygen, is peculiarly associated with one particular item of the body's waste, viz. carbonic acid, in as much as the means which are applied for the introduction of the former are also used for the getting rid of the latter. Both are gases, and the ingress of the one as well as the egress of the other is far more dependent on the simple physical process of diffusion than on any active vital processes carried on by means of tissues. Oxygen passes from the air into the blood mainly by diffusion, and mainly by diffusion also from the blood into the tissues; in the same way carbonic acid passes mainly by diffusion from the tissues into the blood, and from the blood into the air. Whereas, as we have seen, in the secretion of the digestive juices the epithelium-cell plays an all-important part, in respiration the entrance of oxygen from the lungs into the blood, and from the blood into the tissue, and the passage of carbonic acid in the contrary direction, are affected, if at all, in a wholly subordinate manner, by the behaviour of the pulmonary, or of the capillary epithelium. What we have to deal with in respiration then is not so much the vital activities of any particular tissue, as the various mechanisms by which a rapid interchange between the air and the blood is effected, the means by which the blood is enabled to carry oxygen and carbonic acid to and from the tissues, and the manner in which the several tissues take oxygen from and give carbonic acid up to the blood. We have reasons for thinking that oxygen can be taken into the blood, not only from the lungs, but also to a certain small extent from the skin, and, as we have seen, from the alimentary canal also; and carbonic acid certainly passes away from the skin, and through the various secretions, as well as by the lungs. Still the lungs are so eminently the channel of the interchange of gases between the body and the air, that in dealing at the present with respiration, we shall confine ourselves entirely to pulmonary respiration, leaving the consideration of the subsidiary respiratory processes till we come to study the secretions of which they respectively form part. We may turn at once to the structure of the lungs and bronchial passages, including in the latter the trachea but leaving the larynx until we come to study the voice.

§ **315**. The lung takes origin as a diverticulum from the alimentary canal, and we may consider it as a large branched specially-modified gland lined with mucous membrane and consisting of a conducting portion and a secreting portion; the trachea, the two bronchi into which this divides, and the numerous bronchia, or smaller passages branching out from these, represent ducts, and the secreting alveoli of an ordinary gland are represented by what we shall presently describe as air-cells or pulmonary alveoli; but it must be borne in mind that, as we have just said, active secretion by the epithelium lining these pulmonary alveoli is reduced to a minimum or possibly absent altogether.

The complex structure of the mammalian lung will be rendered easier of comprehension if we first say a few words on the structure of a much simpler lung, such as that of the newt or the frog.

The lung of the newt is a long oval sac opening by a short single bronchus into a very short trachea. It may, by inflation, be largely distended, and when the pressure is removed collapses and shrinks to a very small bulk. Its walls are therefore highly elastic, in the sense in which we have so often used that word. They consist, like mucous membrane elsewhere, of an epithelium resting on a connective tissue basis. This connective tissue basis, which is very thin when the lung is distended, contains a very large number of elastic fibres of various sizes but mostly small; these give the wall the elasticity just spoken of. The pulmonary artery, carrying venous blood, divides near the neck of the sac into branches which, running in the connective-tissue of the wall, break up into an exceedingly close-set network of capillaries immediately underneath the epithelium. The capillaries are themselves relatively wide but the meshes are very narrow, being in many cases less than the diameter of a capillary. The epithelium over the whole of the sac consists of a single layer of cells, which, except at the neck of the sac, are modified into thin plates in a somewhat peculiar manner. Three or more cells converge together towards the middle of each of the islands or meshes of the capillary network. The nucleus of each cell is placed within the area of the mesh or island near the convergence of the cell with its neighbours, but a large part of the cell stretches over the capillary surrounding the island to meet a similar extension of another cell whose nucleus is placed in the next island. The part of the cell in which the nucleus is placed, though thin, has some little depth, but the part of the cell stretching over the capillary is reduced to the merest film. Hence each island or mesh is occupied by the nuclei and by the thicker parts of two, three or more converging cells, while the capillary network surrounding the island is separated from the interior of the lung by the extremely thin flat expansion of cells belonging to that and to the neighbouring islands. The blood passing through the capillary is in consequence separated from the air in the lung by nothing more than the capillary wall itself and a film, which has not even the thickness of a flat epithelium cell but is only a wing-like extension of a cell itself flat. The capillaries are in fact imbedded as it were in the epithelial layer. By this means the partition between the blood and the air is reduced to almost the narrowest possible limits. Near the neck of the sac the network becomes more open, and at the neck the peculiar epithelium just described somewhat suddenly changes into a single layer of rather short but otherwise ordinary columnar ciliated cells.

The outer part of the connective tissue basis, away from the epithelium, becoming somewhat looser in texture but still richly provided with elastic fibres, contains besides the small arteries and veins belonging to the capillary networks many small bundles of plain muscular fibres, chiefly running in a circular or transverse direction. Small branches of the vagus nerve pass to the lung, running in company with the pulmonary veins; connected with these, towards the upper part of the lung, are numerous small groups of nerve cells. The nerve fibres, which are chiefly non-medullated, though medullated fibres are also present, end probably in the muscular fibres or in the blood vessels. Branched pigment cells are also present.

§ **316**. The lung of the frog repeats, in structure, most of the features of the newt's lung just described, but is more complicated. The cavity of the sac, especially in its upper part, is broken up by a number of partitions or septa projecting into the interior. Each septum is a fold of the wall of the cavity, and consists of a middle basis of connective tissue, covered on each side with epithelium. From these primary septa start in a similar manner secondary septa of a similar structure, projecting into the open chambers or divisions of the whole sac, formed by the primary septa, and dividing these into smaller open chambers; and many of these secondary septa bear in a similar manner similar tertiary septa, dividing the secondary chambers into tertiary chambers, or alveoli. In this way, especially in its upper part, the cavity of the lung is divided into a honeycomb of chambers or alveoli, the smaller or tertiary alveoli opening into the secondary chambers, the secondary into the primary, and the primary into the general cavity of the lung, which in the upper part of the lung is reduced to a central passage surrounded by the honeycomb work of the chambers. In passing down from the upper to the lower part of the lung, we find the septa become fewer, and the honeycomb more open; the tertiary septa soon fail, then the secondary, and at the very bottom or end of the lung even the primary septa are absent.

Each septum consists of a middle basis of connective tissue, rich in elastic elements, provided with close-set networks of capillaries and covered on each side with epithelium, the characters of the epithelium and its relation to the capillaries being much the same as in the newt. Hence in each septum the blood is freely exposed to the air on each side of the septum; and the arrangement of the honeycomb work of the alveoli increases largely the total surface exposed to the air, and so increases the exposure of the blood.

The plain muscular fibres present in the general wall of the lung pass to a certain extent into the septa. As in the newt, at the neck of the sac the peculiar flat 'respiratory' epithelium, for now we may perhaps so call it, changes into ciliated epithelium; traces of ciliated epithelium are also present at the extreme ends of the septa.

§ **317**. Each of the lobes of which the mammalian lung is made up, may be seen, at times somewhat indistinctly, to be divisible into lobules. The *bronchia*, or divisions of the right and left bronchus respectively, dividing dichotomously, and running between the lobules as interlobular bronchia, accompanied by branches of the pulmonary artery and pulmonary veins, finally plunge into and end in lobules as 'lobular' bronchia. Within the lobules the lobular bronchia divide in a more or less rectangular manner into smaller 'intralobular' bronchia or *bronchioles*, often spoken of also as *alveolar passages*. Each such bronchiole ends in an enlargement having more or less the form of an inverted cone, called an *infundibulum*. Each infundibulum repeats to a certain extent the structure of the whole lung of the frog, or rather is intermediate between the lung of the frog and that of the newt. The more or less conical chamber of the infundibulum narrowing into its bronchiole is divided by a number of septa into secondary chambers of a somewhat polygonal form, the septa being simple and not as in the frog bearing secondary and tertiary septa. Each of these secondary chambers is called an *alveolus;* it has a base which is part of the wall of the infundibulum, sides which are formed by the septa, and a mouth which opens into the general cavity of the infundibulum and so into the bronchiole. Similar but less developed septa are projected into the more tubular cavity of the bronchiole itself, dividing it, less completely, into alveoli; hence the name alveolar passage; these wholly disappear before the bronchiole on its way out from the lobule becomes a definite bronchium.

Each infundibulum is surrounded by connective tissue carrying blood vessels and lymphatics. A number of infundibula with their respective bronchioles are bound together by connective tissue carrying larger blood vessels to form a lobule, the bronchioles joining to form the lobular bronchia. A number of lobules are bound together with interlobular bronchia and still larger blood vessels to form a lobe, and several lobes join to form the lung. When a lung is inflated, and when as after death the blood vessels are for the most part emptied of blood, the infundibula with their alveoli form by far the greater part of the bulk of the lung. Hence a section taken through a hardened and prepared inflated lung seems to be made up almost wholly of a number of polygonal or frequently hexagonal spaces, which are sections of alveoli, and among which are seen sections in various planes of bronchia, small and large, and of blood vessels; here and there the section may disclose the opening of a bronchiole into an infundibulum, and the division of one of the lobular bronchia into a number of bronchioles.

§ **318**. The infundibulum repeats in structure as we have said the lung of the newt or the frog. A septum or wall between two contiguous alveoli consists of a thin median basis of connective tissue, crowded with a close-set capillary network, and covered on each side with an epithelium. The connective tissue is richly provided with fine elastic fibres, but the ordinary gelatiniferous fibrillæ are imperfectly developed, the blood vessels being to a large extent imbedded as it were in a homogeneous matrix. The septum, especially towards its summit, is often so thin that the capillary is exposed to the air on both sides. The cells of the epithelium, which is much better shewn in the lung of a young animal, and indeed is in the adult very difficult to see, are for the most part transformed into small flat transparent plates from which the nuclei have disappeared; their outlines may be distinctly shewn by silver nitrate treatment but otherwise are often very indistinct. Between these clear flat plates there occur small groups of cells distinguished by possessing nuclei, and by their cell-substance being granular and staining with the ordinary reagents. These granular cells, which are thicker than the clear plates, are placed in groups in the meshes of the capillary networks, so that the capillaries themselves are covered only by the thin nucleus-less plates.

The wall of the infundibulum which forms the bases of the several alveoli has a similar structure, and is lined with an epithelium of similar character, the chief difference between the sides and the base of an alveolus being that while the blood in the capillaries of the latter is exposed to the air of the alveolus on one side only, that of the former is often exposed on both sides of even the same capillary.

§ **319**. In describing the bronchial passages we had perhaps better begin with the trachea.

The trachea consists of a ciliated mucous membrane, resting on a coat of connective tissue, strengthened with hoops or imperfect rings of cartilage and provided with a certain amount of plain muscular tissue. A vertical section of the mucous membrane shews an epithelium consisting of three or more layers of cells, those in the uppermost layer being columnar ciliated cells (§ 93), and those in the lower layers small rounded cells, the cell-substance being scanty in proportion to the nucleus; it is supposed that some of these small cells may at times develope into ciliated cells in order to replace loss. Among ciliated cells are seen a certain number of goblet cells (§ 261). Beneath the epithelium runs a fairly distinct basement membrane, and below this in turn is seen some fine reticular tissue, like that in the small intestine (§ 259), containing in its meshes a certain number of leucocytes. Mixed up with the reticular tissue, which in different animals varies much in the amount present, are seen a certain but variable number of fine elastic fibres. These structures constitute together the mucous membrane, below which is a somewhat conspicuous layer of elastic fibres, arranged more or less in a network, but running distinctly longitudinally and forming a longitudinal elastic layer separating the mucous membrane above from the loose submucous connective tissue below. In this submucous tissue are placed a number of small mucous or albuminous glands, like those of the œsophagus, the ducts of which passing through the elastic layer, reticular tissue and epithelium, open into the canal of the trachea. The outer part of this submucous tissue forms a somewhat denser coat of connective tissue, in which are lodged hoops of hyaline cartilage, that is to say, rings which are imperfect behind. Stretching transversely between the ends of each hoop of cartilage are several bundles of plain muscular fibres, completing the ring as it were by a muscular band; a few longitudinally disposed muscular bundles may also be seen outside the transverse bundles. These two sets of muscular fibres may be taken as being the remains of the original complete double muscular coat of the alimentary canal, almost obliterated by the introduction of the cartilaginous hoops.

The main purpose served by these several structures is to provide a wide flexible elastic tube, the bore of which remains large and open and the lining smooth during the bending of the tube. The mucous fluid secreted by the goblet cells and small glands helps to arrest solid particles carried in by the inspired air, while the cilia are continually driving that mucus, with the particles entangled in it, upwards to the larynx and so into the mouth. The elastic layer adapts the mucous membrane to the variations in the length of the tube during its bending, and so keeps it smooth. The transverse muscles by contracting can somewhat narrow the bore, when required; but their effect in this direction can be slight only.

§ **320**. In passing from the trachea to the bronchi and larger bronchia, the chief changes to be observed are that the cartilages are no longer in the form of regular hoops, but are plates placed irregularly, becoming smaller and more irregular in disposition the smaller the tube, and that the transverse muscular fibres become more and more prominent, forming a distinct circular coat of some thickness. The cartilages, supported by a fibrous coat of connective tissue, lie entirely outside the muscular coat, and the small glands have their ducts lengthened so that the bodies of the glands instead of lying in the submucous tissue, lie outside the muscular layer which is pierced by their ducts. The tube becomes now distinctly a muscular tube, though the patency of its bore and a certain amount of rigidity combined with flexibility is still secured by the scattered plates and flakes of cartilage. After death, owing to the contraction of the circular muscular fibres, the mucous membrane, like the internal coat of an artery in the same circumstances, is thrown into longitudinal folds.

In the smaller bronchia the cartilages disappear altogether, and the tube then consists of an outer coat of connective tissue with abundant elastic fibres and a considerable number of circularly disposed muscular fibres, and an inner coat of mucous membrane with its own elastic layer; the supply of small glands still continues.

As one of these bronchia plunging into a lobule divides into bronchioles, the columnar cells of the mucous membrane lose their cilia, become shorter so as to be cubical, and are disposed in a single layer or at most in two layers only. At the same time the muscular fibres become more scanty, and are disposed not as a continuous coat but in scattered rings, the connective tissue coat becomes thinner, and the glands disappear.

In the bronchioles themselves as they prepare to open into infundibula, the epithelium cells become flat though still retaining granular cell-bodies. Among these however may now be seen patches in which the cells are flat transparent plates, many of which do not possess a nucleus; and towards the infundibulum these patches increase in number until the epithelium assumes the character which we previously described as characteristic of the alveoli. The muscular fibres disappear or spread out longitudinally, and the previously compact layer of elastic fibres now becomes scattered and spread out over the alveoli of the infundibulum and bronchiole. In this way the structure of the bronchiole gradually merges into that of an alveolus.

§ **321**. In an infundibulum and in each of its constituent alveoli what we may consider as the original wall of a pulmonary passage, namely, a mucous membrane separated by submucous connective tissue from a muscular coat, is reduced to a thin sheet of connective tissue in which bundles of fibrillæ are scanty or even absent, and which is rather to be considered as a membrane of homogeneous nature containing imbedded in itself a large number of elastic fibres and fibrils with a few connective tissue corpuscles, and a network of capillaries so close set that the membrane seems to be merely elastic material filling up the meshes of the network. On the outside, this capillary membrane, if we may so call it, is continuous with the looser ordinary connective tissue, still however containing abundant elastic elements, which carries the small arteries and veins going to and coming from the capillary network, and which unites the infundibula and bronchioles into lobules. On the inside lies the attenuated epithelium, all the cells of which are flat and some of which are mere nucleus-less plates. The muscular fibres have either wholly disappeared or, according to some observers, persist as a few straggling fibres spreading over the infundibulum. The terminal portion of the pulmonary passage is a sac, whose walls are reduced to almost the greatest possible thinness consistent with their retaining very great elastic power.

The bronchial passages of medium size are essentially elastic muscular tubes, capable like the arteries of varying their calibre, but unless their muscular fibres are thrown into unusually powerful contractions, remaining always fairly open; the smaller ones however, those which are devoid of cartilage, may perhaps close by collapse. These passages are lined by mucous membrane, the cells of which are well formed and active, some secreting mucus, and others by their cilia driving that mucus onwards towards the trachea. The air which passes into the lungs is frequently laden with impurities, these are entangled in the mucus of the passages, especially the smaller ones, and so are either carried upwards in the mucus, or as we shall see otherwise disposed of.

The larger passages are open flexible tubes becoming more rigidly open, and less susceptible to change in calibre by muscular contraction the larger they are.

§ **322**. The lungs are well provided with lymphatics. The reticular tissue underlying the epithelium of the mucous membrane is here and there developed into masses of true adenoid tissue crowded with leucocytes, that is to say, into more or less completely differentiated lymphatic follicles, and similar follicles are met with in deeper parts. Among the flat polygonal epithelioid plates which form the surface of the pleural membrane investing the lung are numerous stomata (§ 290); and during the rhythmic movements of the lungs in breathing the lymph or serous fluid of the pleural cavity is continually being pumped into the lymphatic vessels of the lungs. These lymphatic vessels, arising from lymph-spaces in all parts of the lungs including the connective tissue around the alveoli, and running in the connective tissue binding together infundibula, bronchial tubes and blood vessels into lobules, and the lobules into lobes, find their way at last, after traversing several lymphatic (bronchial) glands to the roots of the lungs, whence they pass from the left lung to the thoracic duct, and from the right lung to the right lymphatic trunk.

The impurities in the inspired air spoken of above as arrested in the mucus lining the bronchial passages often make their way through the epithelium into the lymphatics below and, carried away in the lymph stream, are often retained in the bronchial lymphatic glands. At times these glands become in this way loaded with particles of carbon.

The blood vessels of the lungs do not call for any special comment save perhaps that the pulmonary veins are destitute of valves; and that special arteries, the bronchial arteries, starting from the aorta, are distributed to the walls of the bronchial passages, to the blood vessels, to the lymphatic glands and to the sub-pleural tissue, the blood returning from them along the bronchial veins into the right vena azygos on the right side, and into the superior intercostal vein on the left side.

§ **323**. The nerves to the lungs come chiefly from the vagus. As, on each side, the vagus nerve winds round the root of the lung, it gives off in front branches to form the anterior pulmonary plexus, and then, behind, stouter branches to form the posterior pulmonary plexus. Both these, but especially the latter, are joined by filaments from the sympathetic system, more especially from the second, third, and fourth thoracic ganglia; and it is maintained by some that fibres pass direct from the spinal (intercostal) nerves into these pulmonary plexuses. The upper part of the trachea is supplied by twigs from the recurrent laryngeal nerve on each side, and the lower part by twigs, (tracheal branches) coming direct from the vagus trunks.

Some of the nerve fibres thus reaching the lung along the vagus nerve are efferent fibres for the muscular fibres of the bronchial passages and trachea. But, as we shall see, the chief and most important fibres are afferent fibres concerned in the regulation of respiration. The functions of the fibres coming from the sympathetic system have not yet been clearly ascertained; but there is evidence that some of the fibres coming from the thoracic ganglia are vaso-motor (constrictor) fibres for the pulmonary vessels.

SEC. 2. THE MECHANICS OF PULMONARY RESPIRATION.

§ **324**. The lungs are placed, in a state which is always one of distension, sometimes greater, sometimes less, in the air-tight thorax, the cavity of which they, together with the heart, great blood vessels and other organs, completely fill. By the contraction of certain muscles the cavity of the thorax is enlarged. The lungs must follow this enlargement and be themselves enlarged; otherwise the pleural cavities would be enlarged, but this is impossible so long as the walls are intact. The enlargement of the lung consists chiefly in an enlargement or expansion of the pulmonary alveoli, the air in which becomes by the expansion rarified. That is to say the pressure of the air within the lungs becomes less than that of the air outside the body; and this difference of pressure causes a rush of air through the trachea into the lungs until an equilibrium of pressure is established between the air inside the lungs and that outside. This constitutes inspiration. Upon the relaxation of the inspiratory muscles (the muscles whose contractions have brought about the thoracic expansion), the elasticity of the lungs and chest-walls, aided perhaps to some extent by the contraction of certain muscles, causes the chest to return to its original size; in consequence of this the pressure within the lungs now becomes greater than that outside, and thus air rushes out of the trachea until equilibrium is once more established. This constitutes expiration; the inspiratory and expiratory act together forming a respiration. The fresh air introduced into the upper part of the pulmonary passages by the inspiratory movement contains more oxygen and less carbonic acid than the old air previously present in the lungs. By diffusion the new or *tidal* air, as it is frequently called, gives up its oxygen to, and takes carbonic acid from, the old or *stationary* air, as it has been called, and thus when it leaves the chest in expiration has been the means of both introducing oxygen into the chest and of removing carbonic acid from it. In this way, by the ebb and flow of the tidal air, and by diffusion between it and the stationary air, the whole air in the lungs is being constantly renewed through the alternate expansion and contraction of the chest.

§ **325**. In ordinary respiration, the expansion of the chest never reaches its maximum; by more forcible muscular contractions, by what is called laboured inspiration, an additional thoracic expansion can be brought about, leading to the inrush of a certain additional quantity of air before equilibrium is established. This additional quantity is often spoken of as *complemental* air. In the same way, in ordinary respiration, the contraction of the chest never reaches its maximum. By calling into use additional muscles, by a laboured expiration, an additional quantity of air, the so-called *reserve* or *supplemental* air, may be driven out. But even after the most forcible expiration, a considerable quantity of air, the *residual* air, still remains in the lungs. The natural condition of the lungs in the chest is in fact one of partial distension. The elastic pulmonary tissue is always to a certain extent on the stretch; it is always, so to speak, striving to pull asunder the pulmonary from the parietal pleura; but this it cannot do, because the air can have no access to the pleural cavity. When, however, the chest ceases to be air-tight, when by a puncture of the chest-wall or diaphragm, air is freely introduced into the pleural chamber, the elasticity of the lungs pulls the pulmonary away from the parietal pleura, and the lungs collapse, driving out by the windpipe a considerable quantity of the residual air. Even then, however, the lungs are not completely emptied, some air still remaining in them; this is probably air imprisoned in the infundibula by collapse of the bronchioles, which as we have seen have flaccid and not rigid walls. If in a living animal the pressure of the atmosphere continue to have access to the outside of a lung the air thus imprisoned is gradually absorbed and the lung becomes solid. The same result may occur from the pressure of fluid accumulated in the pleural cavity.

It need hardly be added that when the pleura is punctured, and air can gain *free* admittance from the exterior into the pleural chamber, since the resistance to the entrance of the air into the pleural chamber is far less than the resistance to the entrance into the lungs, the effect of the respiratory movements is simply to drive air in and out of that chamber, instead of in and out of the lung. There is in consequence no renewal of the air within the lungs under those circumstances. If there be a sufficient obstacle to the entrance of air into the pleural chamber, such as a fold of tissue blocking up the opening, the expansion of the chest may still lead to a distension of the lungs; and in this way in some cases puncture of the chest walls has not seriously interfered with respiration. The parietal and pulmonary pleura are, in normal circumstances, separated by a very thin layer only of fluid, so that we may perhaps speak of them as being in a state of 'adhesion,' such as obtains between two wet membranes superimposed. And it has been suggested that this adhesion, having to be overcome before the two surfaces can separate, assists in preventing the entrance of air into the pleural cavity after puncture of the thorax; but it has not been clearly shown that this is really of importance in the matter.

§ **326**. Before birth the lungs contain no air; they are in the condition called *atelectatic*. The walls of the alveoli, the epithelial lining of which is at that time well developed, consisting of distinctly nucleated cells with granular cell-substance, are in contact, the cavity of the alveolus not having as yet come into existence; the walls of the bronchioles are similarly in a collapsed condition, with their walls touching; the more rigid bronchia, like the trachea, possess some amount of lumen which, however, is occupied by fluid. When the chest expands with the first breath taken, the pressure of the inspired air has to overcome the "adhesion," obtaining between the walls of the alveoli thus in contact with each other and also those of the bronchioles. The force spent in thus opening out and unfolding, so to speak, the alveoli and bronchioles is considerable, and in the expiration succeeding the first inspiration most of the air thus introduced remains, the force exerted by the chest in returning to its previous dimensions after the breathing in, and the elastic action of the alveoli being insufficient to bring the walls of the alveoli again into contact. Succeeding breaths unfold the lungs more and more until all the alveoli and bronchioles are opened up, and then the whole force of the expiratory act is directed to driving out the previously inspired air.

It is not, however, until sometime after birth that the lungs pass into that further distended state of which we spoke above. In a newly-born animal there is no negative pressure obtaining in the pleural cavities, the lungs when at rest are not on the stretch, and opening the thorax does not lead to collapse of the lungs. The state of things obtaining later on is established, not at once but gradually, and is apparently brought about by the thorax growing more rapidly, and so becoming relatively more capacious than the lungs. The distension of the lungs in the adult may be familiarly described as being due to the chest being too large for the lungs.

§ **327**. In man the pressure exerted by the elasticity of the lungs alone amounts to about 5 or 7 mm. of mercury. This is estimated by tying a manometer into the windpipe of a dead subject and observing the rise of mercury which takes place when the chest-walls are punctured. If we took 7·6 mm. as the pressure, this would be just 1/100 of the pressure of the atmosphere. If the chest be forcibly distended beforehand, a much larger rise of the mercury is observed, amounting, in the case of a distension corresponding to a very forcible inspiration, to 30 mm. In the living body this mechanical elastic force of the lungs may be assisted by the contraction of the plain muscular fibres of the bronchi; the pressure, however, which can be exerted by these probably does not exceed 1 or 2 mm.

When a manometer is introduced into a lateral opening of the windpipe of an animal, the mercury will fall, indicating a negative pressure as it is called, during inspiration, and rise, indicating a positive pressure, during expiration, both fall and rise being slight and varying according to the freedom with which the air passes in and out of the chest. When a manometer is fitted with air-tight closure into the mouth, or better, in order to avoid the suction-action of the mouth, into one nostril, the other nostril and the mouth being closed, and efforts of inspiration and expiration are made, the mercury falls or undergoes negative pressure with inspiration, and rises, or undergoes positive pressure during expiration. It has been found in this way that the negative pressure of a strong inspiratory effort may vary from 30 to 74 mm., and the positive pressure of a strong expiration from 62 to 100 mm.

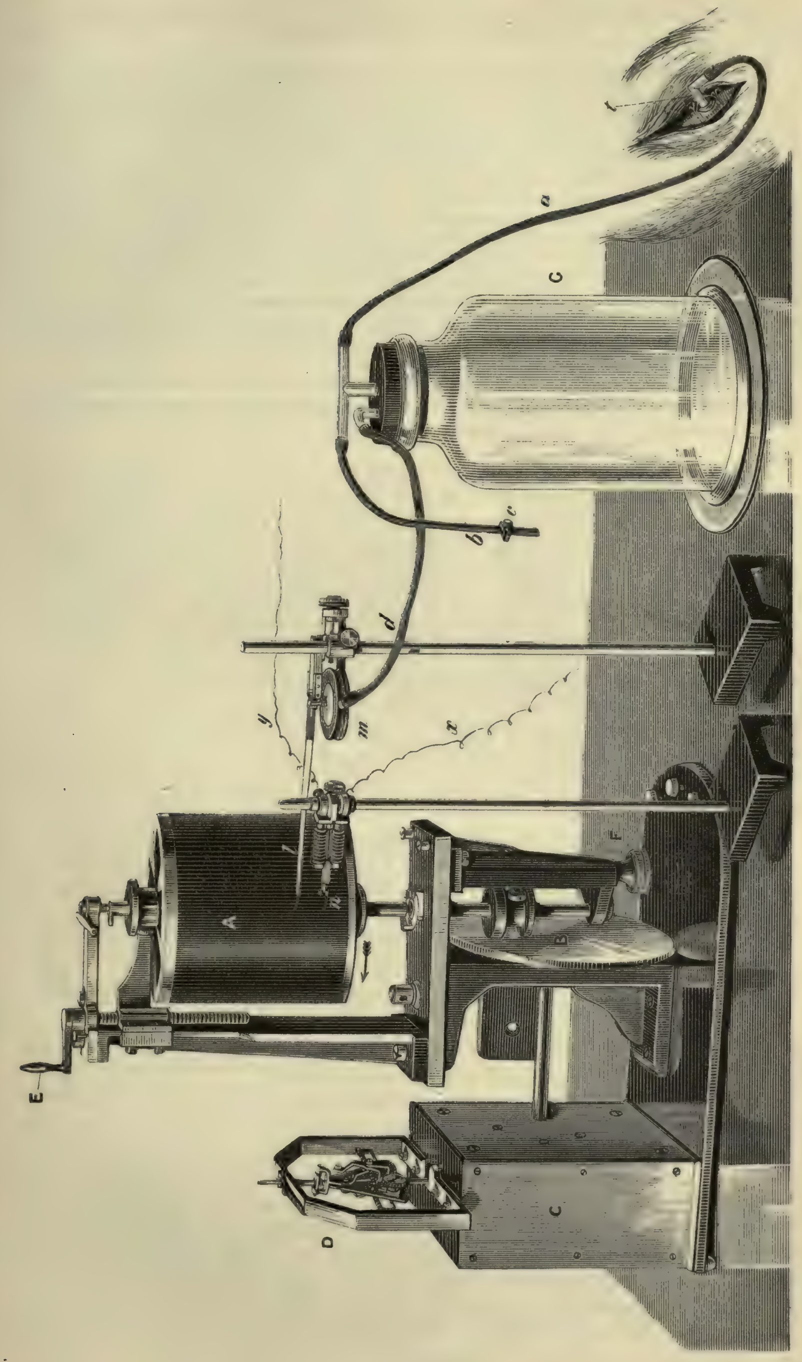
The total amount of air which can be given out by the most forcible expiration following upon a most forcible inspiration, that is, the sum of the complemental, tidal and reserve airs, has been called 'the vital capacity;' 'extreme differential capacity' is a better phrase. It may be measured by a modification of a gas-meter called a *spirometer;* and though it varies largely, the average may be put down at 3—4000 c.c. (200 to 250 cubic inches).

Of the whole measure of vital capacity, about 500 c.c. (30 c. inch) may be put down as the average amount of tidal air, the remainder being nearly equally divided between the complemental and reserve airs. The quantity left in the lungs after the deepest expiration amounts to about 1400 or 2000 c.c.

Since the respiratory movements are so easily affected by various circumstances, the simple fact of attention being directed to the breathing being sufficient to cause modifications both of the rate and depth of the respiration, it becomes very difficult to fix the volume of an average breath. Thus various authors have given figures varying from 53 c.c. to 792 c.c. The statement made above is the mean of observations varying from 177 to 699 c.c.

§ **328.** *Graphic Records of Respiratory Movements.* These may be obtained in many various ways.

The simplest, readiest and perhaps the most generally useful method is that of recording the movements of the column of air. This may be effected by introducing a **T** piece into the trachea, one cross piece being left open, and the other connected with a Marey's tambour or with a receiver which in turn is connected with a tambour, see Fig. 37, and Fig. 71. The movements of the column of air in the trachea are transmitted to the tambour, the consequent expansions and contractions of which are transmitted to the recording drum by means of a lever resting on it.


f
a
C
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D

Fig. 71. Apparatus for taking Tracings of the Movements of the Column of Air in Respiration.

The recording apparatus shewn is the ordinary cylinder recording apparatus. The cylinder A covered with smoked paper is by means of the friction-plate B put into revolution by the spring clock-work in C regulated by Foucault's regulator D. By means of the screw E, the cylinder can be raised or lowered, and by means of the screw F its speed may be increased or diminished.

The tracheotomy tube *t* fixed in the trachea of an animal is connected by india-rubber tubing *a* with a glass T piece inserted into the large jar G. From the other end of the T piece proceeds a second piece of tubing *b*, the end of which can be either closed or partially obstructed at pleasure by means of the screw clamp *c*. From the jar proceeds a third piece of tubing *d*, connected with a Marey's tambour *m* (see Fig. 37), the lever of which *l* writes on the recording surface. When the tube *b* is open the animal breathes freely through this, and the movements in the air of G and consequently in the tambour are slight. On closing the clamp *c*, the animal breathes only the air contained in the jar, and the movements of the lever of the tambour become consequently much more marked.

Below the lever is seen a small time-marker *n* connected with an electro-magnet, the current through which coming from a battery by the wires *x* and *y* is made and broken by a clock-work or metronome.

If, a receiver being used, the open end of the ⊢ be closed, the animal breathes into and out of the receiver, and the movements of the tambour are greatly increased. This has the disadvantage that the air in the receiver soon becomes unfit for further respiration. A similar increase of the movements of the lever of the tambour may be obtained by connecting a piece of india-rubber tubing to the open end of the ⊢. By increasing the length of this tube, or slightly constricting it, the movements of the lever may be increased without very seriously interfering with the breathing of the animal.

In another method the movements of the chest are recorded. When a small animal such as a rabbit is used, the whole animal may be placed in an air-tight box, breathing being carried on by means of a tube inserted into the trachea and carried through an air-tight orifice in the wall of the box. By another orifice and tube the air in the box is brought into connection with a tambour, which accordingly registers the changes of pressure in the air of the box produced by the movements of the chest (and body) and thus indirectly the movements of the chest. In man and larger animals the changes in the girth of the chest may be conveniently recorded by means of Marey's pneumograph. This consists of a hollow elastic cylinder, or a cylinder with elastic ends, the interior of which is connected with a tambour. By means of a strap attached to each end of the cylinder the instrument can be buckled round the chest like a girdle. When the chest expands, the ends of the cylinder are pulled out, and the air within the chamber rarefied; in consequence the lever of the tambour connected with its interior is depressed; conversely, when the chest contracts, the lever is elevated. The pneumatograph of Fick is somewhat similar. Or changes in one or other diameter of the chest may be recorded by what may be called the 'callipers' method, as in the recording stethometer of Burdon-Sanderson. This consists of a rectangular framework constructed of two rigid parallel bars joined at right angles to a cross piece. The free ends of the bars, the distance between which can be regulated at pleasure, are armed, the one with a tambour, the other simply with an ivory button. The tambour bears on the metal plate of its membrane (*m′* Fig. 37) a small ivory button in place of the lever. When it is desired to record the changes occurring in any diameter of the chest, *e.g.* an antero-posterior diameter from a point in the sternum to a point in the back, the instrument is made to encircle the chest somewhat after the fashion of a pair of callipers, the ivory button at one free end being placed on the spine of a vertebra behind and the tambour at the other on the sternum in front in the line of the diameter which is being studied. The distance between the free ends of the instrument being carefully adjusted so that the button of the tambour presses lightly on the sternum, any variations in the length of the diameter in question will, since the framework of the tambour is immobile, give rise to variations of pressure within the tambour. These variations of the 'receiving' tambour as it is called are conveyed by a flexible tube containing air to a second or 'recording' tambour, the lever of which records the variations on a travelling surface. For the purpose of measuring the extent of the movements the instrument must be experimentally graduated. Other forms of callipers may of course be used.

By still another method the variations in intra-thoracic pressure, by means of which the movements of the chest walls produce the movement of air in the lungs, may be recorded. This may be effected by introducing carefully, to the total exclusion of air, into a pleural cavity, or into the pericardial cavity, a cannula connected by a rigid tube with a manometer. With each inspiration a negative pressure, or rather an increase of the existing negative pressure, is produced, the mercury, or fluid, in the manometer returning at each expiration. An easier method of recording this intra-thoracic pressure is to introduce into the œsophagus an elastic sound (similar to the cardiac sound Fig. 37) connected with a tambour. The œsophagus within the thorax like the heart and great vessels, as we shall see, is affected as well as the lungs by the variations of intra-thoracic pressure brought about by the respiratory movements.

In yet another method the movements of the diaphragm which, as we shall see, serve as the prime agent in bringing about the enlargement of the thoracic cavity are recorded. This may be done by inserting, through an incision in the abdominal wall, a flat elastic bag between the diaphragm and abdominal organs. When in inspiration the diaphragm descends it exerts on the bag a pressure which, by means of a tube, may be communicated to a tambour. Or a needle may be thrust through the chest wall so as to rest upon or transfix the diaphragm, and the head of the needle outside the body connected by a thread or otherwise with a lever; each upward and downward movement of the head of the needle, corresponding to the downward and upward movements of the diaphragm, is registered by the lever.

Various modifications of these several methods have been adopted by various observers. They all, however, leave much to be desired. A very ingenious method of registering the contractions of the diaphragm has recently been introduced. In the rabbit two slips of muscular fibres forming part of the diaphragm, one on each side of the ensiform cartilage, are so disposed and possess such attachments that one, or both of them, may be isolated, without injury to either nerves or blood-vessels, and arranged so that while one end of the slip is securely fixed to the chest wall as a fixed point, the other end can by a thread be brought to bear on a lever. The slip, even when thus arranged, appears to contract rhythmically in complete unison with the contractions of the whole rest of the diaphragm ; it serves so to speak as a sample of the diaphragm ; and hence its contractions like those of the whole diaphragm may be taken as a record of respiratory movements. The record has to be corrected for variations in the position of the fixed point.

§ **329**. In these various ways curves are obtained, which, while differing in detail, exhibit the same general features, and more or less resemble the curve shewn in Fig. 72.

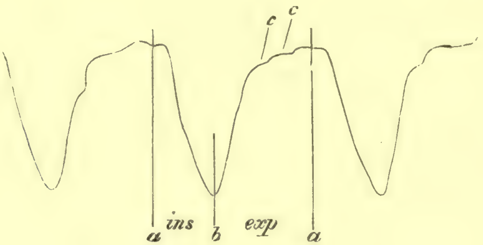

Fig. 72. Tracing of Thoracic Respiratory Movements obtained by means of Marey's Pneumograph.

A whole respiratory phase is comprised between a and a; inspiration, during which the lever *descends*, extending from a to b, and expiration from b to a. The undulations at c are caused by the heart's beat.

As the figure shews, inspiration begins somewhat suddenly and advances rapidly, being followed immediately by expiration, which is carried out at first rapidly, but afterwards more and more slowly. Such pauses as are seen usually occur between the end of expiration and the beginning of inspiration. In normal breathing, hardly any such pause exists, but in cases where the respiration becomes infrequent, pauses of considerable length may be observed. As we shall see in detail hereafter, the several parts of the whole act vary much, under various circumstances, in relation to each other. Sometimes expiration, sometimes inspiration is prolonged ; and either inspiration or expiration may be slow or rapid in its development. At times the chest may remain for a while at the height of inspiration, thus making a pause between inspiration and expiration.

In what may be considered as normal breathing, the respiratory act is repeated about 17 times a minute, the duration of the inspiration as compared with that of the expiration (and such pause as may exist) being about as ten to twelve ; but the rate varies very largely ; and in this as in the volume of each breath it is very difficult to fix a satisfactory average, the figures given varying from 20 to 13 a minute. It varies according to age and sex. It is influenced by the position of the body, being quicker in standing than in lying, and in lying than in sitting. Muscular exertion and emotional conditions affect it deeply. In fact, almost every event which occurs in the body may influence it. We shall have to consider in detail hereafter the manner in which these influences are brought to bear.

When the ordinary respiratory movements prove insufficient to effect the necessary changes in the blood, their rhythm and character become changed. Normal respiration gives place to laboured respiration, and this in turn to *dyspnœa*, which, unless some restorative event occurs, terminates in *asphyxia*. These abnormal conditions we shall study more fully hereafter.

The Respiratory Movements.

§ 330. When the movements of the chest during normal breathing are watched, or when a graphic record is taken by one or other of the methods just described, it is seen that during inspiration an enlargement takes place in the antero-posterior diameter, the sternum being thrown forwards, and at the same time moving upward. The lateral width of the chest is also increased. The vertical increase of the cavity is not so obvious from the outside, though when the movements of the diaphragm are watched by means of an inserted needle or otherwise, it is clear that the upper surface of that organ descends at each inspiration, the anterior walls of the abdomen bulging out at the same time. In the female human subject, the movement of the upper part of the chest is very conspicuous, the breast rising and falling with every respiration; in the male, however, the movements are almost entirely confined to the lower part of the chest. In laboured respiration all parts of the chest are alternately expanded and contracted, the breast rising and falling as well in the male as in the female. We have now to consider these several movements in greater detail, and to study the means by which they are carried out.

§ 331. *Inspiration.* There are two chief means by which the chest is enlarged in normal inspiration, viz. the descent of the diaphragm and the elevation of the ribs. The former causes that movement in the lower part of the chest and abdomen so characteristic of male breathing, which is hence called diaphragmatic; the latter causes the movement of the upper chest characteristic of female breathing, which is called costal. These two main factors are assisted by less important and subsidiary events.

Even in the female human subject, the share taken in respiration by the diaphragm is an important one, in the male the diaphragm must be regarded as the chief respiratory agent, and in some animals its use, for this purpose, is so prominent that the movements of the ribs may in normal breathing be almost neglected. In the rabbit for instance, in normal breathing, almost all the respiratory work is done by the contractions of the diaphragm.

The descent of the diaphragm is effected by means of the contraction of its muscular fibres. When at rest the diaphragm presents a convex surface to the thorax; when contracted it becomes much flatter, and in consequence the level of the chest-floor is lowered, the vertical diameter of the chest being proportionately enlarged. In descending, the diaphragm presses on the abdominal viscera, and so causes a projection of the flaccid abdominal walls. From its attachments to the sternum and the false ribs, the diaphragm, while contracting, naturally tends to pull the sternum and the upper false ribs downwards and inwards, and the lower false ribs upwards and inwards, towards the lumbar spine. In normal breathing, this tendency produces little effect, being counteracted by the accompanying general costal elevation, and by certain special muscles to be mentioned presently. In forced inspiration, however, and especially where there is any obstruction to the entrance of air into the lungs, the lower ribs may be so much drawn in by the contraction of the diaphragm, that the girth of the trunk at this point is obviously diminished.

§ **332**. The elevation of the ribs is a much more complex matter than the descent of the diaphragm. If we examine any one rib, such as the fifth, we find that while it moves freely on its vertebral articulation, it inclines when in the position of rest in an oblique direction from the spine to the sternum; hence it is obvious that when the rib is raised, its sternal attachment must not only be carried upward, but also thrown forward. The rib may in fact be regarded as a radius, moving on the vertebral articulation as a centre, and causing the sternal attachment to describe an arc of a circle in the vertical plane of the body; as the rib is carried upwards from an oblique to a more horizontal position, the sternal attachment must of necessity be carried farther away in front of the spine. Since all the ribs have a downward slanting direction, they must all tend, when raised towards the horizontal position, to thrust the sternum forward, some more than others according to their slope and length. The elasticity of the sternum and costal cartilages, assisted by the articulation of the sternum to the clavicle above, permits the front surface of the chest to be thus thrust forwards as well as upwards, when the ribs are raised. By this action, the antero-posterior diameter of the chest is enlarged.

Since the ribs form arches which increase in their sweep as one proceeds from the first downwards as far at least as the seventh, it is evident that when a lower rib such as the fifth is elevated so as to occupy or to approach towards the position of the one above it, the chest at that level will become wider from side to side, in proportion as the fifth arch is wider than the fourth. Thus the elevation of the rib increases not only the antero-posterior but also the transverse diameter of the chest. Further, on account of the resistance of the sternum, the angles between the ribs and their cartilages are, in the elevation of the ribs, somewhat opened out, and thus also the transverse as well as the antero-posterior diameter, somewhat increased. In more than one way, then, the elevation of the ribs enlarges the dimensions of the chest.

§ **333**. The ribs are raised by the contraction of certain muscles. Of these the external intercostals are perhaps the most important. Even in the case where two ribs, such as the fifth and sixth, are isolated from the rest of the thoracic cage, by section of the structures occupying the intercostal spaces above and below, the contraction of the external intercostal muscle of the intervening space raises the two ribs, thus bringing them towards the position in which the fibres of the muscle have the shortest length, viz. the horizontal one. This elevating action is, in the entire chest, further favoured by the fact that the first rib is less moveable than the second, and so affords a comparatively fixed base for the action of the muscles between the two, the second in turn supporting the third, and so on, while the scaleni muscles in addition serve to render fixed, or to raise, the first two ribs. So that in normal respiration, the act may probably be described as beginning by a contraction of the scaleni. The first two ribs being thus raised or at least fixed, the contraction of the series of external intercostal muscles acts at a great advantage.

While the elevating, *i.e.* inspiratory action of the external intercostals is admitted by nearly all authors, the function of the internal intercostals has been much disputed. Some regard their action as wholly inspiratory; others maintain, what is perhaps the more commonly adopted view, that while those parts of them which lie between the sternal cartilages act like the external intercostals as elevators, *i.e.* as inspiratory in function, those parts which lie between the osseous ribs act as depressors, *i.e.* as expiratory in function.

In the well-known model consisting of two rigid bars, representing the ribs, moving vertically by means of their articulations with an upright representing the spine, and connected at their free ends by a piece representing the sternum, it is undoubtedly true that stretched elastic bands attached to the bars in such a way as to represent respectively the external and internal intercostals, viz. sloping in the one case downwards and forwards and in the other downwards and backwards, do, on being left free to contract, in the former case elevate and in the latter depress the ribs. Such a model however does not fairly represent the natural conditions of the ribs, which are not straight and rigid, but peculiarly curved and of varying elasticity, capable moreover of rotation on their own axes, and having their movements determined by the characters of their vertebral articulations. The mechanical conditions in fact of these muscles are so complex, that a deduction of their actions from simple mechanical principles, or from the direction of the fibres, must be exceedingly difficult and dangerous. Actual experiments on the cat and dog tend to shew that in these animals the contraction of the internal intercostals, along their whole length, takes place, in point of time, alternately with that of the diaphragm, and thus afford an argument in favour of these muscles being expiratory in function.

Next in importance to the external intercostals come the levatores costarum, which, though small muscles, are able, from the nearness of their costal insertions to the fulcrum, to produce considerable movement of the sternal ends of the ribs. The external intercostals and the levatores costarum with the scaleni may fairly be said to be the elevators of the ribs, *i.e.* the chief muscles of costal inspiration in normal breathing.

It must be added however that some observers deny that either set of intercostal muscles take any important part in raising the ribs. They hold that the chief if not the only use of these muscles is by their contraction to render the intercostal spaces firm and the whole thoracic cage rigid, so that the thorax is moved as a whole by the other muscles mentioned, and the intercostal spaces do not give way during the respiratory movements.

Additional space in the transverse diameter is afforded probably by the rotation of the ribs on an antero-posterior axis; but this movement is quite subsidiary and unimportant. When the chest is at rest, the ribs are somewhat inclined with .their lower borders directed inwards as well as downwards. When they are drawn up by the action of the intercostal muscles, their lower borders are everted. Thus their flat sides are presented to the thoracic cavity, which is thereby slightly increased in width.

§ **334**. *Laboured Inspiration.* When respiration becomes laboured, other muscles are brought into play. The scaleni are strongly contracted, so as distinctly to raise or at least give a very fixed support to the first and second ribs. In the same way the serratus posticus superior, which descends from the fixed spine in the lower cervical and upper dorsal regions to the second, third, fourth, and fifth ribs, by its contractions raises those ribs. In laboured breathing a function of the lower false ribs, not very noticeable in easy breathing, comes into play. They are depressed, retracted, and fixed, thereby giving increased support to the diaphragm, and directing the whole energies of that muscle to the vertical enlargement of the chest. In this way the serratus posticus inferior, which passes upward from the lumbar aponeurosis to the last four ribs, by depressing and fixing those ribs becomes an adjuvant inspiratory muscle. The quadratus lumborum and lower portions of the sacro-lumbalis may have a similar function.

All these muscles may come into action even in breathing which, though deeper than usual, can hardly perhaps be called laboured. When, however, the need for greater inspiratory efforts becomes urgent, all the muscles which can, from any fixed point, act in enlarging the chest, come into play. Thus the arms and shoulder being fixed, the serratus magnus passing from the scapula to the middle of the first eight or nine ribs, the pectoralis minor passing from the coracoid to the front parts of the third, fourth, and fifth ribs, the pectoralis major passing from the humerus to the costal cartilages, from the second to the sixth, and that portion of the latissimus dorsi which passes from the humerus to the last three ribs, all serve to elevate the ribs and thus to enlarge the chest. The sterno-mastoid and other muscles passing from the neck to the sternum, are also called into action. In fact, every muscle which by its contraction can either elevate the ribs or contribute to the fixed support of muscles which do elevate the ribs, such as the trapezius, levator anguli scapulæ and rhomboidei by fixing the scapula, may, in the inspiratory efforts which accompany dyspnœa, be brought into play.

§ **335**. *Expiration.* In normal easy breathing, expiration is in the main a simple effect of elastic reaction. By the inspiratory effort the elastic tissue of the lungs is put on the stretch; so long as the inspiratory muscles continue contracting, the tissue remains stretched, but directly those muscles relax, the elasticity of the lungs comes into play and drives out a portion of the air contained in them. Similarly the elastic sternum and costal cartilages are by the elevation of the ribs put on the stretch: they are driven into a position which is unnatural to them. When the intercostal and other elevator muscles cease to contract, the elasticity of the sternum and costal cartilages causes them to return to their previous position, thus depressing the ribs, and diminishing the dimensions of the chest. When the diaphragm descends, in pushing down the abdominal viscera, it puts the abdominal walls on the stretch: and hence, when at the end of inspiration the diaphragm relaxes, the abdominal walls return to their place, and by pressing on the abdominal viscera, push the diaphragm up again into its position of rest. Expiration then during easy breathing is, in the main, simple elastic reaction; but there is probably some, though possibly in most cases, a very slight, expenditure of muscular energy to bring the chest more rapidly to its former condition. This is, as we have seen, supposed by many to be afforded by the internal intercostals acting as depressors of the ribs. If these do not act in this way, we may suppose that the elastic return of the abdominal walls is accompanied and assisted by a contraction of the abdominal muscles. The triangularis sterni, the effect of whose contraction is to pull down the costal cartilages, may also be regarded as an expiratory muscle.

When expiration becomes laboured, the abdominal muscles become important expiratory agents. By pressing on the contents of the abdomen, they thrust them and therefore the diaphragm also up towards the chest, the vertical diameter of which is thereby lessened, while by pulling down the sternum and the middle and lower ribs they lessen also the cavity of the chest in its antero-posterior and transverse diameters. They are, in fact, the chief expiratory muscles, though they are doubtless assisted by the serratus posticus inferior and portions of the sacro-lumbalis, since when the diaphragm is not contracting, the depression of the lower ribs which the contraction of these muscles causes, serves only to narrow the chest. As expiration becomes more and more forced, every muscle in the body which can either by contracting depress the ribs, or press on the abdominal viscera, or afford fixed support to muscles having those actions, is called into play.

§ **336**. *Facial and Laryngeal Respiration.* The thoracic respiratory movements are accompanied by associated respiratory movements of other parts of the body, more particularly of the face and of the glottis.

In normal healthy respiration the current of air which passes in and out of the lungs, travels, not through the mouth but through the nose, chiefly through the lower nasal meatus. The ingoing air, by exposure to the vascular mucous membrane of the narrow and winding nasal passages, is more efficiently warmed than it would be if it passed through the mouth; and at the same time the mouth is thereby protected from the desiccating effect of the continual inroad of comparatively dry air.

During each inspiratory effort the nostrils are expanded, probably by the action of the dilatores naris, and thus the entrance of air facilitated. The return to their previous condition during expiration is effected by the elasticity of the nasal cartilages, assisted perhaps by the compressores naris. This movement of the nostrils, perceptible in many people even during tranquil breathing, becomes very obvious in laboured respiration.

When the mouth is closed, the soft palate which is held somewhat tense, is swayed by the respiratory current, but entirely in a passive manner, and it is not until the larynx is reached by the ingoing air that any active movements are met with. When the larynx (the details of which we shall have to deal with at a later part of this work) is examined with the laryngoscope, it is frequently seen that, while during inspiration the glottis is widely open, with each expiration the arytenoid cartilages approach each other so as to narrow the glottis, the cartilages of Santorini projecting inwards at the same time. Thus, synchronous with the respiratory expansion and contraction of the chest, and the respiratory elevation and depression of the alæ nasi, there is a rhythmic widening and narrowing of the glottis. Like the movements of the nostril, this respiratory action of the glottis is much more evident in laboured than in tranquil breathing. Indeed in the latter case it is frequently absent. The manner in which this rhythmic opening and narrowing is effected will be described when we come to study the production of the voice. Whether there exists a rhythmic contraction and expansion of the trachea and bronchial passages, especially the smaller and more exclusively muscular ones, effected by means of the plain muscular tissue of those organs and synchronous with the respiratory movements of the chest, is uncertain.

SEC. 3. CHANGES OF THE AIR IN RESPIRATION.

§ **337**. During its stay in the lungs, or rather during its stay in the bronchial passages, the tidal air (by means of diffusion chiefly) effects exchanges with the stationary air; in consequence the expired air differs from inspired air in several important particulars.

The temperature of expired air is variable, but under ordinary circumstances is higher than that of the inspired air. At an average temperature of the atmosphere, for instance at about 20° C., the temperature of expired air is, in the mouth 33·9°, in the nose 35·3°. When the external temperature is low, that of the expired air sinks somewhat, but not to any great extent, thus at – 6·3° C. it is 29·8° C. When the external temperature is high, the expired air may become cooler than the inspired, thus at 41·9° it has been found to be 38·1°. The expired air takes its temperature from that of the body, that is, of the blood, and this as we shall see later on while generally higher may, at times, be lower than that of the atmosphere. The exact temperature of the expired air in fact depends on the relative temperatures of the blood and inspired air, and on the depth and rate of breathing. The change in temperature takes place not in the lungs but in the upper passages, and chiefly in the nose and pharynx.

§ **338**. The expired air is loaded with aqueous vapour. The point of saturation of any gas, that is, the utmost quantity of water which any given volume of gas can take up as aqueous vapour, varies with its temperature, being higher with the higher temperature. For its own temperature expired air is, according to most observers, saturated with aqueous vapour. The moisture, like the warmth, is imparted not in the depths of the lung but in the upper passages. The inspired air as it passes into the bronchia is already saturated with moisture.

§ **339**. The expired air contains about 4 or 5 p.c. less oxygen, and about 4 p.c. more carbonic acid than the inspired air, the quantity of nitrogen suffering but little change. Thus

	oxygen.	nitrogen.	carbonic acid.
Inspired air contains	20·81	79·15	·04
Expired „ „	16·033	79·587	4·38

The quantity of nitrogen in the expired air is sometimes found to be slightly greater than, as in the table above, but sometimes equal to, and sometimes less than, that of the inspired air.

In a single breath the air is richer in carbonic acid (and poorer in oxygen) at the end than at the beginning of the breath. Hence the longer the breath is held, the greater the (artificial) pause between inspiration and expiration, the higher the percentage of carbonic acid in the expired air. Thus by increasing the interval between two expirations to 100 seconds, the percentage may be raised to 7·5. When the rate of breathing remains the same, by increasing the depth of the breathing the percentage of carbonic acid in each breath is lowered, but the total quantity of carbonic acid expired in a given time is increased. Similarly, when the depth of breath remains the same, by quickening the rate the percentage of carbonic acid in each breath is lowered, but the quantity expired in a given time is increased.

Taking, as we have done, the amount of tidal air passing in and out of the chest of an average man at 500 c.c., such a person will expire about 22 c.c. of carbonic acid at each breath; this, reckoning the rate of breathing at 17 a minute, would give over 500 litres of carbonic acid for the day's production. Actual determinations however give a rather smaller total than this; thus in a series of experiments of which we shall have to speak hereafter, the total daily excretion of carbonic acid in an average man was found to be 800 grms., *i.e.* rather more than 400 litres (406), containing 218·1 grms. carbon, and 581·9 grms. oxygen, the oxygen which actually disappeared from the inspired air at the same time being about 700 grms. This amount it should be said represents, owing to the manner in which the experiment was conducted, the gases given out and taken in, not by the lungs only, but by the whole body; but the amount of carbonic acid given out by other channels than the lungs is, as we shall see, very slight (10 grms. or even less), so that 800 grms. may be taken as the average production of carbonic acid by an average man. The quantity however, both of oxygen consumed and of carbonic acid given out, is subject to very wide variations; thus in the observations of which we are speaking the daily quantity of carbonic acid varied from 686 to 1285 grms., and that of the oxygen from 594 to 1072 grms. These variations and their causes will be discussed when we come to deal with the problems of nutrition.

§ **340**. When the total quantity of tidal air given out at any expiration is compared with that taken in at the corresponding inspiration, it is found that, both being dried and measured at the same temperature and pressure, the expired air is less in volume than the inspired air, the difference amounting to about $\frac{1}{40}$th or $\frac{1}{50}$th of the volume of the latter. Hence, when an animal is made to breathe in a confined space, the air is absolutely diminished in volume. The approximate equivalence in volume between inspired and expired air arises from the fact that the volume of any given quantity of carbonic acid is equal to the volume of the oxygen consumed to produce it; the slight falling short of the expired air is due to the circumstance that all the oxygen inspired does not reappear in the carbonic acid expired, some having formed within the body other combinations.

§ **341**. Besides carbonic acid, expired air contains various substances which may be spoken of as impurities, many of an unknown nature, and all in small amounts. Traces of ammonia have been detected in expired air, even in that taken directly from the trachea, in which case its presence could not be due to decomposing food lingering in the mouth. When the expired air is condensed by being conveyed into a cooled receiver, the aqueous product is found to contain organic matter, which, from the presence of micro-organisms, introduced in the inspired air, is very apt rapidly to putrefy. The organic substances thus shewn to be present in the expired air are the cause in part of the odour of breath. It is probable that some of them are of a poisonous nature, either poisonous in themselves as coming direct from and produced in some way or other in the pulmonary apparatus, or poisonous as being the products of putrefactive decomposition; for various animal substances and fluids give rise by decomposition to distinct poisonous products, known as *ptomaines*, and it is possible that some of the constituents of expired air are of an allied nature. In any case the substances present have a deleterious action, for an atmosphere containing simply 1 p.c. of carbonic acid (with a corresponding diminution of oxygen) has very little effect on the animal economy, whereas an atmosphere in which the carbonic acid has been raised to 1 p.c. by breathing, is highly injurious. In fact, air rendered so far impure by breathing that the carbonic acid amounts to ·08 p.c. is distinctly unwholesome, not so much on account of the carbonic acid, as of the accompanying impurities. Since these impurities are of unknown nature and cannot be estimated, the easily determined carbonic acid is usually taken as an indirect measure of their presence. We have seen that the average man loads, at each breath, 500 c.c. of air with carbonic acid to the extent of 4 p.c. He will accordingly at each breath load 2 litres to the extent of 1 p.c.; and in one hour, if he breathe 17 times a minute, will load rather more than 2000 litres to the same extent. At the very least then a man ought to be supplied with this quantity of air hourly; and if the air is to be kept fairly wholesome, that is with the carbonic acid reduced considerably below ·1 p.c., he should have even more than ten times as much.

SEC. 4. THE RESPIRATORY CHANGES IN THE BLOOD.

§ 342. While the air in passing in and out of the lungs is thus robbed of a portion of its oxygen, and loaded with a certain quantity of carbonic acid, the blood as it streams along the pulmonary capillaries undergoes important correlative changes. As it leaves the right ventricle it is venous blood of a dark purple or maroon colour; when it falls into the left auricle it is arterial blood of a bright scarlet hue. In passing through the capillaries of the body from the left to the right side of the heart, it is again changed from the arterial to the venous condition. We have to inquire, What are the essential differences between arterial and venous blood, by what means is the venous blood changed into arterial in the lungs, and the arterial into venous in the rest of the body, and what relations do these changes in the blood bear to the changes in the air which we have already studied?

The facts, that venous blood at once becomes arterial in appearance on being exposed to or shaken up with air or oxygen, and that arterial blood becomes venous in appearance when kept for some little time in a closed vessel, or when submitted to a current of some indifferent gas such as nitrogen or hydrogen, prepare us for the statement that the fundamental difference between venous and arterial blood is in the relative proportion of the oxygen and carbonic acid gases contained in each. From both, a certain quantity of gas can be extracted by means which do not otherwise materially alter the constitution of the blood; and this gas when obtained from arterial blood is found to contain more oxygen and less carbonic acid than that obtained from venous blood. This is the real differential character of the two bloods; all other differences are either, as we shall see to be the case with the colour, dependent on this, or are unimportant and fluctuating.

If the quantity of gas which can be extracted by the mercurial air-pump from 100 vols. of blood be measured at 0° C., and a pressure of 760 mm., it is found to amount, in round numbers, to 60 vols.

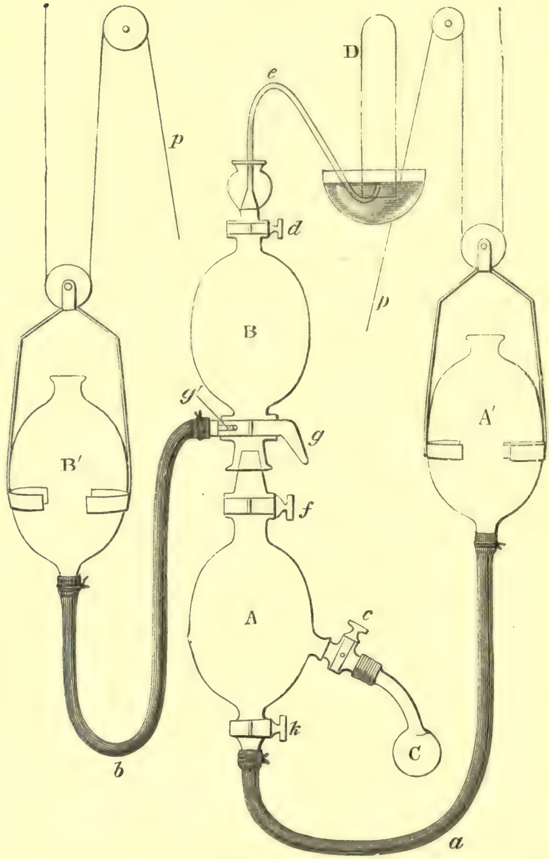

Fig. 73. Diagrammatic Illustration of Ludwig's Mercurial Gas-Pump.

A and B are two glass globes, connected by strong india-rubber tubes, *a* and *b*, with two similar glass globes A′ and B′. A is further connected by means of the stopcock *c* with the receiver C containing the blood (or other fluid) to be analysed, and B by means of the stopcock *d* and the tube *e* with the receiver D for receiving the gases. A and B are also connected with each other by means of the stopcocks *f* and *g*, the latter being so arranged that B also communicates with B′ by the passage *g′*. A′ and B′ being full of mercury and the cocks *k*, *f*, *g*, and *d* being open but *c* and *g′* closed, on raising A′ by means of the pulley *p* the mercury of A′ fills A, driving out the air contained in it, into B, and so out through *e*. When the mercury has risen above *g*, *f* is closed, and *g′* being opened, B′ is in turn raised till B is completely filled with mercury, all the air previously in it being driven out through *e*. Upon closing *d*, and lowering B′, the whole of the mercury in B falls in B′, and a vacuum consequently is established in B. On closing *g′*, but opening *g*, *f*, and *k* and lowering A′, a vacuum is similarly established in A and in the junction between A and B. If the cock *c* be now opened the gases of the blood in C escape into the vacuum of A and B. By raising A′, after the closure of *c*, and opening of *d*, the gases so set free are driven from A into B, and by the raising of B′ from B, through *e* into the receiver D, standing over mercury.

The vacuum produced by the ordinary mechanical air-pump is insufficient to extract all the gas from blood. Hence it becomes necessary to use a mercury pump capable of producing a large Torricellian vacuum. In the form of mercurial pump which bears Ludwig's name (Fig. 73) two large globes of glass, one fixed and the other moveable, are connected by a flexible tube; the fixed globe is made to communicate by means of air-tight stopcocks alternately with a receiver containing the blood, and with a receiver to collect the gas. When the moveable globe filled with mercury is raised above the fixed one, the mercury from the former runs into and completely fills the latter, the air previously present being driven out. After adjusting the cocks, the moveable globe is then depressed thirty inches below the fixed one, in which the consequent fall of the mercury produces an almost complete vacuum. By turning the proper cock this vacuum is put into connection with the receiver containing the blood, which thereupon becomes proportionately exhausted. By again adjusting the cocks and once more elevating the moveable globe, the gas thus extracted is driven out of the fixed globe into a receiver. The vacuum is then once more established and the operation repeated as long as gas continues to be given off from the blood.

A modified form of pump working on the same principles as that of Ludwig, but involving the use of only one globe to be made vacuous and one moveable reservoir for mercury, has been constructed by Pflüger. It presents several advantages over the one just described, the chief being that (i) non-defibrinated blood may be used for the extraction of its gases, (ii) the vacuum into which the gases are evolved is large, (iii) this vacuum is kept dry by being connected laterally with a vacuous chamber containing sulphuric acid. The details of its construction are however complicated, and the greatest care is required in its use to avoid breakage. Of later years a simplified form of pump has been introduced for laboratory work. It was first used by Gréhant and Paul Bert, and is now frequently called an Alvergniat's pump, from the name of its present maker. Fig. 74 gives a diagrammatic representation of its construction.

A is a glass bulb some five inches in diameter, blown on to a glass tube *a* below and on to a vertical tube *b* above. The lower end of *a* is connected by a thick-walled india-rubber tube with a reservoir for mercury *B*, which can be raised and lowered by means of a string passing over a pulley *c*. The vertical tube *b* is thickened at one place, and into this thickened portion a three-way tap *d* is ground. The upper end of *b* is prolonged (above the three-way tap) into a fine point. This point passes by a tight joint through the bottom of a vessel *e*, which can be partly filled with mercury, and over which a receiver *f*, filled with mercury for the collection of the gases, can be inverted. A tube *g* fused on laterally to one opening of the three-way tap *d* places the latter in connection with a thick-walled Woulff's bottle *C* containing a layer of strong sulphuric acid. The second tubulure of this bottle is similarly connected by an elastic tube with the vessel *D*, into which blood or other fluid may be introduced by means of the tap *h*. All the moveable joints of the apparatus are protected by india-rubber tubes into which water can be poured, and a metal casing round the tap *d*, which may also be filled with water, similarly prevents the possibility of any leakage here.

The pump is used as follows. By placing the tap *d* in the position shewn in the figure and raising *B*, the bulb *A* may be filled with mercury up to the top, the contained air being expelled through the upper end of *b*. By a slight turn of the tap all connection between *A* and either the tube *g* or the upper part of *b* may be cut off, and on lowering *B* a vacuum is established in the bulb *A* and part of the tube *a*. *A* may now be connected by the tap *d* with the tube *g*, and hence with *C* and *D*, and, *h* being closed, a partial vacuum is established in *C* and *D*. By means of the tap *d* the air in *A* may be cut off from *g*, and on raising *B* and placing the plug of *d* as shewn in the figure this air may be expelled through the upper end of *b*. By slightly turning *d* and lowering *B* a vacuum is again established in *A*, and as before a further portion of air in *C* and *D* may be allowed to pass over into *A* and the vacuum in *D* and *C* increased. In this way all the air in *D* can be extracted, the final stages being facilitated by the admission of a little water into *D*, the last traces of air being driven over into *A* by the rush of vapour from the water. A known volume of blood having been collected over mercury in a small tube is now allowed to enter *D* through the tap *h* and yields up its gases to the vacuum. A repetition

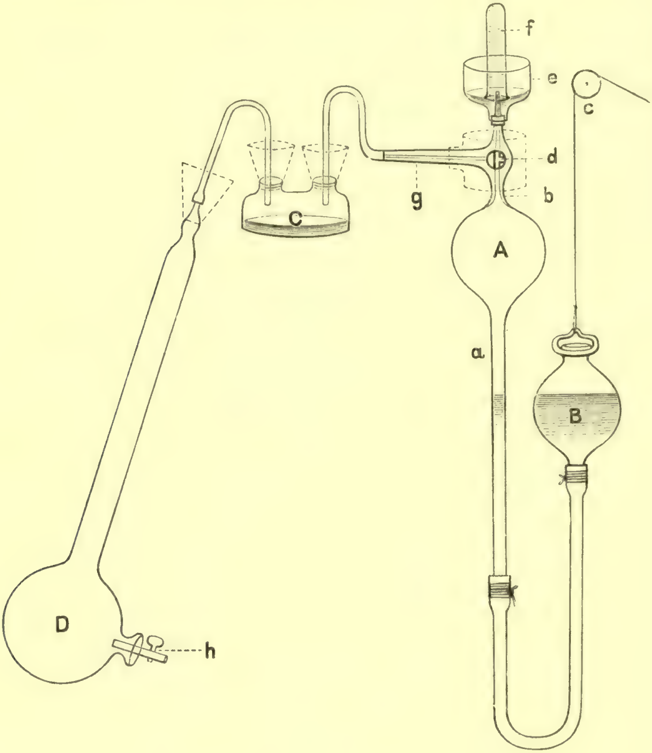

Fig. 74. Diagram of Alvergniat's Pump.

of the processes by which the air in *D* was originally extracted will now remove the gases which have been given off from the known volume of blood, the only difference being that now the tube *f* filled with mercury is inverted in the trough *e* over the upper end of the tube *b*. In this way the gases originally in *D* are not allowed to escape into the air, as was the case when the apparatus was being originally made vacuous, but are collected in *f* for subsequent analysis. During the extraction of the gases from the blood the bulb *D* is immersed in a vessel of warm water, to facilitate the exit of the gases and, by causing the formation of large quantities of aqueous vapour, to sweep the gases rapidly over into *A*. The sulphuric acid chamber *C* dries the vacuum before the admission of the blood into *D*, and hence makes it more perfect and causes the most complete and rapid evolution of gases from the blood.

The average composition of the gas thus obtained from each of the two kinds of blood (the arterial blood being taken from a large artery, and the venous blood from the right side of the heart) is, stated in round numbers, as follows:

From 100 vols.	may be obtained Of oxygen,	of carbonic acid,	of nitrogen.
Of Arterial Blood,	20 vols.	40 vols.	1 to 2 vols.
Of Venous Blood,	8 to 12 vols.	46 vols.	1 to 2 vols.

all measured at 760 mm. and 0° C.

That is to say, venous blood, as compared with arterial blood, contains 8 to 12 p.c. less oxygen and 6 p.c. more carbonic acid. It must be remembered, however, that while arterial blood from whatever artery taken has always nearly the same proportion of gases, or at all events the same amount of oxygen, the amount of oxygen in venous blood, even when taken from the same vein, may vary a good deal, still more so when it is taken from different veins. The reason of this we shall see hereafter.

It will be convenient to consider the relations of each of these gases separately.

The relations of Oxygen in the Blood.

§ **343**. When a liquid such as water is exposed to an atmosphere containing a gas such as oxygen, some of the oxygen will be dissolved in the water, that is to say, will be absorbed from the atmosphere. The quantity which is so absorbed will depend on the pressure of the oxygen in the atmosphere above; the greater the pressure of the oxygen, the larger the amount which will be absorbed. If the pressure of the whole atmosphere remain the same, at 760 mm. of mercury for instance (the ordinary atmospheric pressure), the pressure of the oxygen may be increased or diminished by increasing or diminishing the proportion of oxygen in the atmosphere. So that with an atmosphere remaining at any given pressure the quantity of oxygen absorbed will depend on the quantity present in that atmosphere. If on the other hand water, already containing a good deal of oxygen dissolved in it, be exposed to an atmosphere containing little or no oxygen, the oxygen will escape from the water into the atmosphere. The oxygen, in fact, which is dissolved in the water, like the oxygen in the atmosphere above, stands at a certain pressure, the amount of pressure depending on the quantity dissolved; and when water containing oxygen dissolved in it is exposed to any atmosphere, the result, that is, whether the oxygen escapes from the water into the atmosphere, or passes from the atmosphere into the water, depends on whether the pressure of the oxygen in the water is greater or less than the pressure of the oxygen in the atmosphere. Hence when water is exposed to oxygen, the oxygen either escapes or is absorbed until equilibrium is established between the pressure of the oxygen in the atmosphere above and the pressure of the oxygen in the water below. This result is, as far as mere absorption and escape are concerned, quite independent of what other gases are present in the water or in the atmosphere. Suppose a half-litre of water was lying at the bottom of a two-litre flask, and that the atmosphere in the flask above the water was one-third oxygen; it would make no difference, as far as the absorption of oxygen by the water was concerned, whether the remaining two-thirds of the atmosphere was carbonic acid, or nitrogen, or hydrogen, or whether the space above the water was a vacuum filled to one-third with pure oxygen. Hence it is said that the absorption of any gas depends on the *partial pressure* of that gas in the atmosphere to which the liquid is exposed. This is true not only of oxygen and water, but of all gases and liquids which do not enter into chemical combination with each other. Different liquids will of course absorb different gases with differing readiness; but, with the same gas and the same liquid, the amount absorbed will depend directly on the partial pressure of the gas in the overlying space. It should be added that the process is much influenced by temperature. Hence, to state the matter generally, the absorption of any gas by any liquid will depend on the nature of the gas, the nature of the liquid, the pressure of the gas, and the temperature at which both stand.

Now it might be supposed, and indeed was once supposed, that the oxygen in the blood was simply dissolved by the blood. If this were so, then the amount of oxygen present in any given quantity of blood exposed to any given atmosphere, ought to rise and fall steadily and regularly as the partial pressure of oxygen in that atmosphere is increased or diminished; the absorption (or escape) of oxygen ought to follow what is known as the Henry-Dalton law of pressures. But this is found not to be the case. If we expose blood containing little or no oxygen to a succession of atmospheres containing increasing quantities of oxygen, we find that at first there is a very rapid absorption of the available oxygen, and then this somewhat suddenly ceases or becomes very small; and if on the other hand we submit arterial blood to successively diminishing pressures, we find that for a long time very little oxygen is given off, and then suddenly the escape becomes very rapid. The absorption of oxygen by blood does not follow the general law of absorption according to pressure. The phenomena on the other hand suggest the idea that the oxygen in the blood is in some particular combination with a substance or some substances present in the blood, the combination being of such a kind that it holds good during a lowering of pressure down to a certain limit, and that then dissociation readily occurs; we may add that this limit is very closely dependent on temperature. It is, however, not to be supposed that as the pressure is lowered, no oxygen whatever is given off from the substance until a certain point is reached, and that at that point the whole store is in an instant dissociated, no more remaining to be given off. The case is rather that while pressure is being lowered down to a certain point, no appreciable dissociation takes place, and that then having begun it increases rapidly with each further lowering of pressure until the whole of the oxygen is given off. During this narrow range, between the first beginning to give off oxygen and the completion of the giving off, the compound of the oxygen with the substance or substances may be spoken of as partly, that is more or less, dissociated. What is the substance or what are the substances with which the oxygen is thus peculiarly combined?

If serum, free from red corpuscles, be used in such absorption experiments, it is found that, as compared with the entire blood, very little oxygen is absorbed, about as much as would be absorbed by the same quantity of water; and such as is absorbed does follow the law of pressures. In natural arterial blood the quantity of oxygen which can be obtained from serum is exceedingly small; it does not amount to half a volume in one hundred volumes of the entire blood to which the serum belonged. It is evident that the oxygen which is present in blood is in some way or other peculiarly connected with the red corpuscles. Now the distinguishing feature of the red corpuscles is the presence of hæmoglobin. We have already seen (§ 24) that this constitutes 90 per cent. of the dried red corpuscles. There can be *à priori* little doubt that this must be the substance with which the oxygen is associated; and to the properties of this body we must therefore direct our attention.

§ **344**. *Hæmoglobin.* When separated from the other constituents of the serum, hæmoglobin appears as a substance, either amorphous or crystalline, readily soluble in water (especially in warm water) and in serum.

Since hæmoglobin is soluble in serum, and since the identity of the crystals observed occasionally within the corpuscles with those obtained in other ways shews that the hæmoglobin as it exists in the corpuscle is the same thing as that which is artificially prepared from blood, it is evident that some peculiar relationship between the stroma and the hæmoglobin must, in natural blood, keep the latter from being dissolved by the serum. Hence in preparing hæmoglobin it is necessary first of all to break up this connection and to set the hæmoglobin free from the corpuscles. This may be done by the addition of water, of ether, of chloroform or of bile salts, or by repeatedly freezing and thawing; blood so treated becomes 'laky,' cf. § 24. It is also of advantage previously to remove the alkaline serum as much as possible so as to operate only on the red corpuscles. The stroma and hæmoglobin being thus separated, a solution of hæmoglobin is the result. The alkalinity of the solution, when present, being reduced by the cautious addition of dilute acetic acid, and the solvent power of the aqueous medium being diminished by the addition of one-fourth its bulk of alcohol, the mixture, set aside in a temperature of 0° C. in order still further to reduce the solubility of the hæmoglobin, readily crystallizes, when the blood used is that of the dog, cat, horse, rat, guinea-pig, &c. In the case of the dog indeed it is simply sufficient to add ether carefully to the blood until it just becomes 'laky,' and then to let it stand in a cool place; the mixture soon becomes a mass of crystals. The crystals may be separated by filtration, redissolved in water and recrystallized.

Hæmoglobin from the blood of the rat, guinea-pig, squirrel, hedgehog, horse, cat, dog, goose, and some other animals, crystallizes readily, the crystals being generally slender four-sided prisms, belonging to the rhombic system, and often appearing quite acicular. The crystals from the blood of the guinea-pig are octahedral, but also belong to the rhombic system; those of the squirrel are six-sided plates. The blood of the ox, sheep, rabbit, pig, and man, crystallizes with difficulty. Why these differences exist is not known; but the composition and the amount of water of crystallization vary somewhat in the crystals obtained from different animals. In the dog, the percentage composition of the crystals has been determined as C. 53·85, H. 7·32, N. 16·17, O. 21·84, S. 0·39, Fe. ·43, with 3 to 4 per cent. of water of crystallization. It will thus be seen that hæmoglobin contains, in addition to the other elements usually present in proteid substances, a certain amount of iron; that is to say, the element iron is a distinct part of the hæmoglobin molecule: a fact which of itself renders hæmoglobin remarkable among the chemical substances present in the animal body.

§ **345**. The crystals, when seen in a sufficiently thick layer under the microscope, have the same bright scarlet colour as arterial blood has to the naked eye; when seen in a mass they naturally appear darker. An aqueous solution of hæmoglobin, obtained by dissolving purified crystals in distilled water, has also the same bright arterial colour. A tolerably dilute solution placed before the spectroscope is found to absorb certain rays of light in a peculiar and characteristic manner. A portion of the red end of the spectrum is absorbed, as is also a much larger portion of the blue end; but what is most striking is the presence of two strongly marked absorption bands, lying between the solar lines D and E. (See Fig. 75.) Of these the one towards the red side, sometimes spoken of as the band *a*, is the thinnest, but the most intense, and in extremely dilute solutions (Fig. 75, 1) is the only one visible; its middle lies at some little distance to the blue side of D. Its position may be more exactly defined by expressing it in wave-lengths. As is well known the rays of light which make up the spectrum differ in the length of their waves, diminishing from the red end, where the waves are longest, to the blue end, where they are shortest. Thus Frauenhofer's line D corresponds to rays having a wave-length of 589·4 millionths of a millimeter. Using the same unit, the centre of this absorption band *a* of hæmoglobin corresponds to the wave-length 578; as may be seen in Fig. 75, where however the numbers of the divisions of the scale indicate only 100,000 of a millimeter. The other, sometimes called *β*, much broader, lies a little to the red side of E, its blueward edge, even in moderately dilute solutions (Fig. 75, 2) coming close up to that line; its centre corresponds to about wave-length 539. Each band is thickest in the middle, and gradually thins away at the edges. These two absorption bands are extremely characteristic of a solution of hæmoglobin. Even in very dilute solutions both bands are visible (they may be seen in a thickness of 1 c.m. in a solution containing 1 grm. of hæmoglobin in 10 litres of water), and that when scarcely any of the extreme red end, and very little of the blue end, is cut off. They then appear not only faint but narrow. As the strength of the solution is increased, the bands broaden, and become more intense; at the same time both the red end, and still more the blue end, of the whole spectrum, are encroached upon (Fig. 75, 3). This may go on until the two absorption bands become fused together into one broad band (Fig. 75, 4). The only rays of light which then pass through the hæmoglobin solution are those in the green between the blueward edge of the united bands and the general absorption which is now rapidly advancing from the blue end, and those in the red between the united bands and the general absorption at the red end. If the solution be still further increased in strength, the interval on the blue side of the united bands becomes absorbed also, so that the only rays which pass through are the red rays lying to the red side of D; these are the last to disappear, and hence the natural red colour of the solution as seen by transmitted light. Exactly the same appearances are seen when crystals of hæmoglobin are examined with a microspectroscope. They are also seen when arterial blood itself (diluted with saline solutions so that the

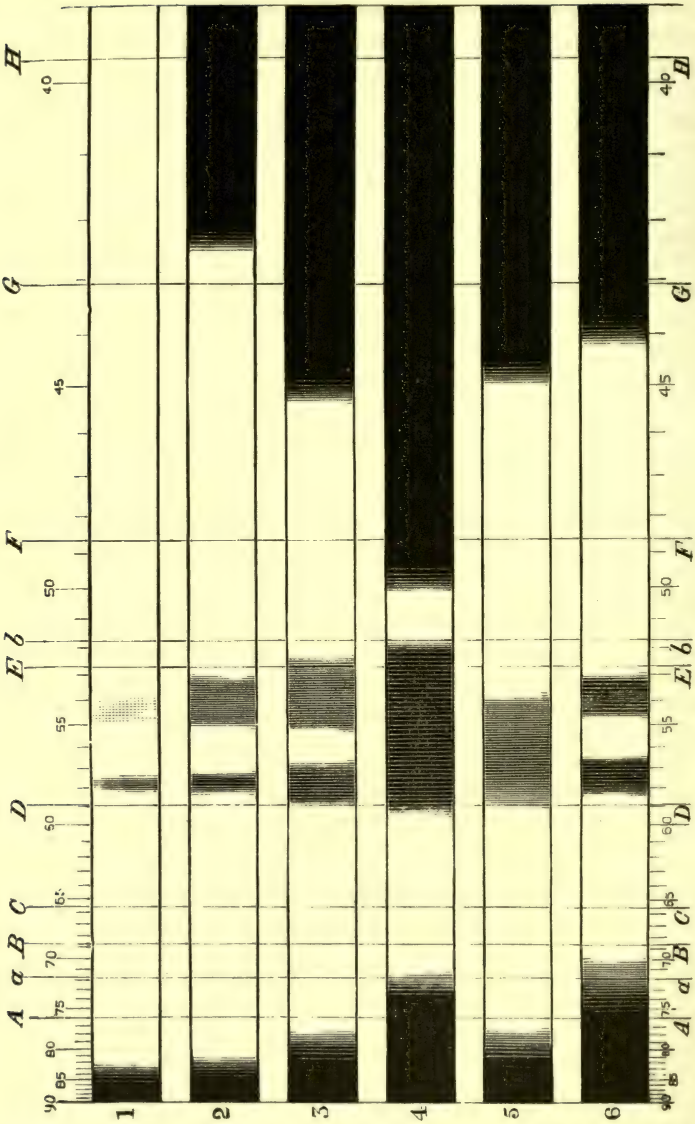

Fig. 75. (After Preyer and Gamgee.) The Spectra of Oxy-Hæmoglobin in different grades of concentration, of (reduced) Hæmoglobin and of Carbonic-Oxide-Hæmoglobin.

1 to 4. Solution of Oxy-Hæmoglobin containing (1) less than ·01 p.c., (2) ·09 p.c., (3) ·37 p.c., (4) ·8 p.c.
5. ,, ,, (reduced) Hæmoglobin containing about ·2 p.c.
6. ,, ,, carbonic oxide Hæmoglobin.

In each of the six cases the layer brought before the spectroscope was 1 c.m. in thickness. The letters (*A*, *a* &c.) indicate Frauenhofer's lines, and the figures wave-lengths expressed in 100,000th of a millimetre.

corpuscles remain in as natural a condition as possible) is examined with the spectroscope, as well as when a drop of blood, which from the necessary exposure to air is always arterial, is examined with the micro-spectroscope. In fact, the spectrum of hæmoglobin is the spectrum of normal arterial blood.

§ **346**. When crystals of hæmoglobin, prepared in the way described above, are subjected to the vacuum of the mercurial air-pump, they give off a certain quantity of oxygen, and at the same time they change in colour. The quantity of oxygen given off is definite, 1 grm. of the crystals giving off 1·59 c.cm. of oxygen measured at 760 mm. Hg and 0° C. In other words, the crystals of hæmoglobin, over and above the oxygen which enters intimately into the composition of the molecule (and which alone is given in the elementary composition previously stated), contain another quantity of oxygen, which is in loose combination only, and which may be dissociated from them by subjecting them to a sufficiently low pressure. The change of colour which ensues when this loosely combined oxygen is removed, is characteristic; the crystals become darker and more of a purple hue, and at the same time dichroic, so that while the thicker ridges are purple, the thin edges appear greenish.

An ordinary solution of hæmoglobin, like the crystals from which it is formed, contains a definite quantity of oxygen in a similarly peculiar loose combination; this oxygen it also gives up when subjected in the air-pump to a sufficiently low pressure, becoming at the same time of a purplish hue. This loosely combined oxygen may also be removed by passing a stream of hydrogen or other indifferent gas through the solution; the stream of hydrogen acts like an oxygen-vacuum to the hæmoglobin and thus dissociation is effected. Carbonic acid gas is unsuitable for this purpose, since, as we shall see, being an acid it acts in another way on the hæmoglobin. The oxygen may also be removed from the hæmoglobin not only by physical but also by chemical means, as by the use of reducing agents. Thus if a few drops of ammonium sulphide or of an alkaline solution of ferrous sulphate, kept from precipitation by the presence of tartaric acid, be added to a solution of hæmoglobin, or even to an unpurified solution of blood corpuscles such as is afforded by the washings from a blood clot, the oxygen in loose combination with the hæmoglobin is immediately seized upon by the reducing agent. This may be recognised at once, by the characteristic change of colour; from a bright scarlet the solution becomes of a purplish claret colour, when seen in any thickness, but greenish when sufficiently thin: the colour of the reduced solution is exactly like that of the crystals from which the loose oxygen has been removed by the air-pump.

Examined by the spectroscope, this reduced solution, or solution of *reduced hæmoglobin,* as we may now call it, offers a spectrum (Fig. 75, 5) very different from that of the unreduced solution.

The two absorption bands have disappeared, and in their place there is seen a single, much broader, but at the same time much fainter band, whose middle occupies a position about midway between the two absorption bands of the unreduced solution, though the redward edge of the band shades away rather farther towards the red than does the other edge towards the blue; its centre corresponds to about wave length 555. At the same time the general absorption of the spectrum is different from that of the unreduced solution; less of the blue end is absorbed. Even when the solutions become tolerably concentrated, many of the bluish-green rays to the blue side of the single band still pass through. Hence the difference in colour between hæmoglobin which retains the loosely combined oxygen[1], and hæmoglobin which has lost its oxygen and become reduced. In tolerably concentrated solutions, or tolerably thick layers, the former lets through the red and the orange-yellow rays, the latter the red and the bluish-green rays. Accordingly, the one appears scarlet, the other purple. In dilute solutions, or in a thin layer, the reduced hæmoglobin lets through so much of the green rays that they preponderate over the red, and the resulting impression is one of green. In the unreduced hæmoglobin or oxyhæmoglobin, the potent yellow which is blocked out in the reduced hæmoglobin makes itself felt, so that a very thin layer of oxyhæmoglobin, as in a single corpuscle seen under the microscope, appears yellow rather than red.

It must be remembered that when we speak of reduced hæmoglobin (or more briefly hæmoglobin), with a purple colour and a characteristic onebanded spectrum, we mean hæmoglobin which has lost *all* its loosely associated oxygen. If a quantity of oxyhæmoglobin be exposed to an insufficiently low pressure, or to the action of an insufficient quantity of the reducing action, it gives up a part only of its oxygen; it is only partly reduced. Such a partly reduced solution still shews the two bands of oxyhæmoglobin.

§ **347.** When the hæmoglobin solution (or crystal) which has lost its oxygen by the action either of the air-pump or of a reducing agent or by the passage of an indifferent gas, is exposed to air containing oxygen, an absorption of oxygen at once takes place. If sufficient oxygen be present, the hæmoglobin seizes upon sufficient oxygen to obtain its full complement, each gramme taking up in combination 1·59 c.cm. of oxygen; if there be an insufficient quantity of oxygen the hæmoglobin still remains partly reduced; or perhaps we may say that a part only of the hæmoglobin gets its allowance while the remainder continues reduced. If the amount of oxygen be sufficient, the solution (or crystal), as it takes up the oxygen, regains its bright scarlet colour and its characteristic absorption spectrum, the single band being replaced by the two. Thus if a solution of oxyhæmoglobin in a test-tube, after being reduced by the action of a drop or two of ammonium sulphide solution and thus shewing the purple colour and the single band, be shaken up with air, the bright scarlet colour at once returns, and when the fluid is placed before the spectroscope, it is seen that the single faint broad band of the reduced hæmoglobin has wholly disappeared, and that in its place are the two sharp thinner bands of the oxyhæmoglobin. If left to stand in the test-tube the quantity of reducing agent still present is generally sufficient again to rob the hæmoglobin of the oxygen thus newly acquired, and soon the scarlet hue fades back again into the purple, the two bands giving place to the one. Another shake and exposure to air will however again bring back the scarlet hue and the two bands; and once more these may disappear. In fact, a few drops of the reducing fluid will allow this game of hæmoglobin taking oxygen from the air and giving it up to the reducer to be played over and over again; at each turn of the game the colour shifts from scarlet to purple, and from purple to scarlet, while the two bands exchange for the one, and the one for the two.

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[1] For brevity's sake we may call the hæmoglobin containing oxygen in loose combination, *oxyhæmoglobin*, and the hæmoglobin from which this loosely combined oxygen has been removed, reduced hæmoglobin or simply hæmoglobin.

§ **348**. *Colour of Venous and Arterial Blood.* Evidently we have in these properties of hæmoglobin an explanation of at least one-half of the great respiratory process, and they teach us the meaning of the change of colour which takes place when venous blood becomes arterial or arterial venous.

In venous blood, as it issues from the right ventricle, the oxygen present is insufficient to satisfy wholly the hæmoglobin of the red corpuscles; the hæmoglobin is, to a large extent, reduced, hence the purple colour of venous blood. When ordinary venous blood, diluted without access of oxygen, is brought before the spectroscope, the two bands of oxyhæmoglobin are seen. This is explained by the fact that in partly reduced hæmoglobin, which we may conveniently regard as a mixture of oxyhæmoglobin and (reduced) hæmoglobin, the two sharp bands of the former are always much more readily seen than the much fainter band of the latter. Now in ordinary venous blood there is always some loose oxygen, removable by diminished pressure or otherwise; the hæmoglobin is only partly reduced, there is always some, indeed a considerable quantity, of oxyhæmoglobin as well as (reduced) hæmoglobin. It is only under special circumstances, as for instance after death by what we shall presently speak of as asphyxia, that all the loose oxygen of the blood disappears; and then the two bands of the oxyhæmoglobin vanish too. If even only a small quantity of oxygen be present so distinct are the two bands that a solution of completely reduced hæmoglobin may be used as a test for the presence of oxygen; if oxygen be present in any fluid to which the reduced hæmoglobin is added, the single band immediately gives way to the two bands of oxyhæmoglobin.

As the venous blood passes through the capillaries of the lungs, this reduced hæmoglobin takes from the pulmonary air its complement of oxygen, all or nearly all the hæmoglobin of the red corpuscles becomes oxyhæmoglobin, and the purple colour forthwith shifts into scarlet. For careful observations shew that the hæmoglobin of arterial blood is saturated or nearly saturated with oxygen; it probably falls short of complete saturation by about 1 vol. of oxygen in 100 vols. of blood. By increasing the pressure of the oxygen, an additional quantity may be driven into the blood, but this, after the hæmoglobin has become completely saturated, is effected by simple absorption. The quantity so added is extremely small compared with the total quantity combined with the hæmoglobin.

Passing from the left ventricle to the capillaries of the tissues the oxyhæmoglobin gives up some of its oxygen to the tissues, becoming, in part, reduced hæmoglobin, and the blood in consequence becomes once more venous, with a purple hue. Thus the red corpuscles by virtue of their hæmoglobin are emphatically oxygen-carriers. Undergoing no intrinsic change in itself, the hæmoglobin combines in the lungs with oxygen, which it carries to the tissues; these, more greedy of oxygen than itself, rob it of its charge, and the reduced hæmoglobin hurries back to the lungs in the venous blood for another portion. The change from venous to arterial blood is then in part (for as we shall see there are other events as well) a peculiar combination of hæmoglobin with oxygen, while the change from arterial to venous is, in part also, a reduction of oxyhæmoglobin; and the difference of colour between venous and arterial blood depends almost entirely on the fact that the reduced hæmoglobin of the former is of purple colour, while the oxyhæmoglobin of the latter is of a scarlet colour.

There may be other causes of the change of colour, but these are wholly subsidiary and unimportant. When a corpuscle swells, its refractive power is diminished, and in consequence the number of rays which pass into and are absorbed by it are increased at the expense of those reflected from its surface; anything therefore which swells the corpuscles, such as the addition of water, tends to darken blood, and anything, such as a concentrated saline solution, which causes the corpuscles to shrink, tends to brighten blood. Carbonic acid has apparently some influence in swelling the corpuscles, and therefore may aid in darkening the venous blood.

§ **349**. We have spoken of the combination of hæmoglobin with oxygen as being a peculiar one. The peculiarity consists in the facts that the oxygen may be associated and dissociated, without any general disturbance of the molecule of hæmoglobin, and that dissociation may be brought about very readily. Hæmoglobin combines in a wholly similar manner with other gases. If carbonic oxide (monoxide) be passed through a solution of hæmoglobin, a change of colour takes place, a peculiar bluish tinge making its appearance. At the same time the spectrum is altered; two bands are still visible, but on accurate measurement it is seen that they are placed more towards the blue end than are the otherwise similar bands of oxyhæmoglobin (see Fig. 75, 6); their centres corresponding respectively to about wave-lengths 572 and 533, while those of oxyhæmoglobin as we have seen correspond to 578 and 539. When a known quantity of carbonic oxide gas is sent through a hæmoglobin solution, it will be found on examination that a certain amount of the gas has been retained, an equal volume of oxygen appearing in its place in the gas which issues from the solution. If the solution so treated be crystallized, the crystals will have the same characteristic colour, and give the same absorption spectrum as the solution; when subjected to the action of the mercurial pump, they will give off a definite quantity of carbonic oxide, 1 grm. of the crystals yielding 1·59 c.cm. of the gas. In fact, hæmoglobin combines loosely with carbonic oxide just as it does with oxygen; but its affinity with the former is greater than with the latter. While carbonic oxide readily turns out oxygen, oxygen cannot so readily turn out carbonic oxide. Indeed, carbonic oxide has been used as a means of driving out and measuring the quantity of oxygen present in any given blood. This property of carbonic oxide explains its poisonous nature. When the gas is breathed, the reduced and the unreduced hæmoglobin of the venous blood unite with the carbonic oxide, and hence the peculiar bright cherry-red colour observable in the blood and tissues in cases of poisoning by this gas. The carbonic oxide hæmoglobin, however, is of no use in respiration; it is not an oxygen-carrier, nay more, it will not readily, though it does so slowly and eventually, give up its carbonic oxide for oxygen, when the poisonous gas ceases to enter the chest and is replaced by pure air. The organism is killed by suffocation, by want of oxygen, in spite of the blood not assuming any dark venous colour; to adopt a phrase which has been used, the corpuscles are paralysed.

Hæmoglobin similarly forms a compound, having a characteristic spectrum, with nitric oxide, more stable even than that with carbonic oxide.

It has been supposed by some that the oxygen thus associated with hæmoglobin is in the condition known as ozone; but the arguments urged in support of this view are inconclusive.

Products of the decomposition of Hæmoglobin.

§ **350.** Although a crystalline body, hæmoglobin diffuses with great difficulty. This arises from the fact that it is in part a proteid body; it consists of a colourless proteid, associated with a coloured substance, which may be separated out from the hæmoglobin, though not in the exact condition in which it naturally exists in the compound; this substance when separated out appears as a brownish-red body known as *hæmatin.* All the iron belonging to the hæmoglobin is in reality attached to the hæmatin. A solution of hæmoglobin, when heated, coagulates, the exact degree at which the coagulation takes place depending on the amount of dilution; at the same time it turns brown from the setting free of the hæmatin. If a strong solution of hæmoglobin be treated with acetic (or other) acid, the same brown colour, from the appearance of hæmatin, is observed. The proteid constituent however is not coagulated, but by the action of the acid passes into the state of acid-albumin. On adding ether to the mixture, and shaking, the hæmatin is dissolved in the supernatant acid ether, which it colours a dark red, and which, examined with the spectroscope, is found to possess a well-marked spectrum, the spectrum of the so-called acid hæmatin of Stokes (Fig. 76, 6). The proteid in the water below the ether appears in a coagulated form owing to the action of the ether. In a somewhat similar manner alkalis split up hæmoglobin into a proteid constituent and hæmatin.

The exact nature of the proteid constituent of hæmoglobin has not as yet been clearly determined. It was supposed to be globulin (hence the name hæmatoglobulin, contracted into hæmoglobin), but though belonging to the globulin family, has characters of its own; it is possibly a mixture of two or more distinct proteids. It has been provisionally named *globin* and is said to be free from ash.

§ **351**. Hæmatin when separated from its proteid fellow, and purified, appears as a dark-brown amorphous powder, or as a scaly mass with a metallic lustre, having the probable composition of C_{32}, H_{34}, N_4, Fe, O_5. It is fairly soluble in dilute acid or alkaline solutions, and then gives characteristic spectra (Fig. 76, 1, 2, 5).

An interesting feature in hæmatin is that its *alkaline* solution is capable of being reduced by reducing agents, the spectrum changing at the same time (Fig. 76, 3), and that the reduced solution will, like the hæmoglobin, take up oxygen again on being brought into contact with air or oxygen. This would seem to indicate that the oxygen-holding power of hæmoglobin is connected exclusively with its hæmatin constituent.

By the action of strong sulphuric acid hæmatin may be robbed of all its iron. It still retains the feature of possessing colour, the solution of iron-free hæmatin being a dark rich brownish red; but is no longer capable of combining loosely with oxygen. This indicates that the iron is in some way associated with the peculiar respiratory functions of hæmoglobin; though it is obviously an error to suppose, as was once supposed, that the change from venous to arterial blood consists essentially in a change from a ferrous to a ferric salt.

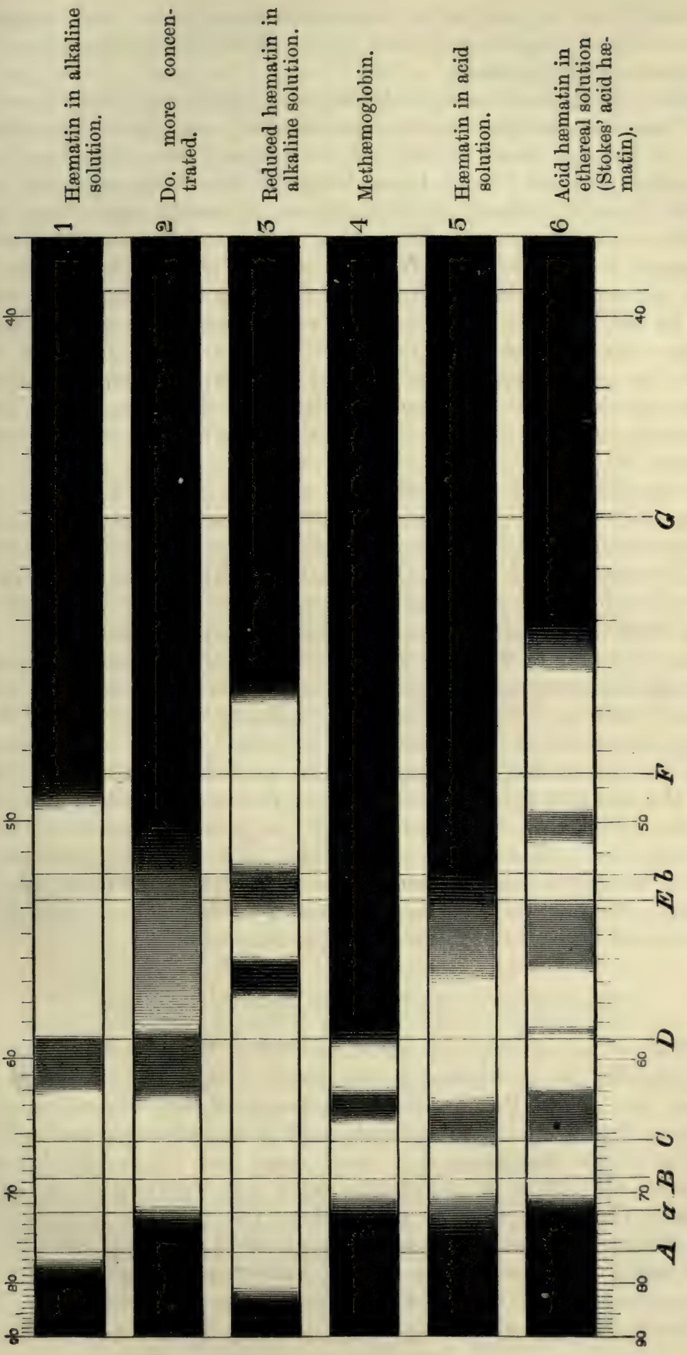
1 Hæmatin in alkaline solution.
2 Do. more concentrated.
3 Reduced hæmatin in alkaline solution.
4 Methæmoglobin.
5 Hæmatin in acid solution.
6 Acid hæmatin in ethereal solution (Stokes' acid hæmatin).
40
50
60
70
80
90
A
a
B
C
D
E
b
F
G

FIG. 76. (After Gamgee.) SPECTRA OF SOME DERIVATIVES OF HÆMOGLOBIN. Compare with Fig. 75.

Though not crystallizable itself, hæmatin forms with hydrochloric acid a compound, occurring in minute rhombic crystals, known as *hæmin* crystals.

When blood is left until it decomposes, the hæmoglobin is very apt to become changed into a peculiar body known as *methæmoglobin,* in the spectrum of which a very conspicuous band is seen in the red between C and D (see Fig. 76, 4). The same change may be brought about by the action of weak acids, such as carbonic acid, by ozone, and by other agents such as nitrites and potassium permanganate. When a stream of carbonic acid is driven through blood or through a solution of hæmoglobin the band in the red characteristic of methæmoglobin soon makes its appearance. Methæmoglobin differs but little if at all in elementary composition from hæmoglobin; it is maintained that it contains the same quantity of oxygen as oxy-hæmoglobin but in a more stable condition, more intimately associated with the molecule.

In conclusion, the condition of oxygen in the blood is as follows. Of the whole quantity of oxygen in the blood, only a minute fraction is simply absorbed or dissolved according to the law of pressures (the Henry-Dalton law). The great mass is in a state of combination with the hæmoglobin, the connection being of such a kind that while the hæmoglobin readily combines with the oxygen of the air to which it is exposed, dissociation readily occurs at low pressures, or in the presence of indifferent gases, or by the action of substances having a greater affinity for oxygen than has hæmoglobin itself. The difference between venous and arterial blood, as far as oxygen is concerned, is that while in arterial blood the hæmoglobin holds nearly its full complement of oxygen and may be spoken of as nearly wholly oxyhæmoglobin, in venous blood the hæmoglobin is to a large but variable extent, reduced; and the characteristic colours of venous and arterial blood are in the main due to the fact that the colour of reduced hæmoglobin is purple, while that of oxyhæmoglobin is scarlet.

The relations of the Carbonic Acid in the Blood.

§ 352. The presence of carbonic acid in the blood appears to be determined by conditions more complex in their nature and at present not so well understood as those which determine the presence of oxygen. The carbonic acid is not simply dissolved in the blood; its absorption by blood does not follow the law of pressures. It exists in association with some substance or substances in the blood, and its escape from the blood is a process of dissociation. We cannot however speak of it as being associated, to the same extent as is the oxygen, with the hæmoglobin of the red corpuscles. So far from the red corpuscles containing the great mass of the carbonic acid, the quantity of this gas which is present in a volume of serum is according to some observers actually greater than that which is present in an equal volume of blood, *i.e.* an equal volume of mixed corpuscles and serum; that is to say, the carbonic acid is much more largely associated with the serum (or, in the living blood, with the plasma) than with the red corpuscles.

When serum is subjected to the action of the mercurial pump, by far the greater part of the carbonic acid is given off; but a small additional quantity (2 to 5 vols. per cent.) may be extracted by the subsequent addition of an acid. This latter portion may be spoken of as 'fixed' carbonic acid in distinction to the larger 'loose' portion which is given off to the vacuum. When however the whole blood is subjected to the vacuum until the carbonic acid ceases to be given off, the subsequent addition of acid is said not to set free any further quantity; so that when serum is mixed with corpuscles all the carbonic acid may be spoken of as 'loose'; and it is stated that the excess of carbonic acid in a quantity of serum over that present in the same bulk of entire blood, corresponds to the fixed portion in serum which has to be driven off by an acid. Moreover, even those who maintain that the quantity of carbonic acid in entire blood is less than that in an equal volume of serum, admit that the carbonic acid exists in some way or other at a higher pressure in, and is more readily given off from entire blood than from serum.

If these statements be accepted it seems probable that the carbonic acid exists associated with some substance or substances in the serum, or rather plasma, but that the conditions of its association (and therefore of its dissociation) are determined by the action of some substance or substances present in the corpuscles. It has been suggested that the association of the carbonic acid in the plasma is with one or other of the proteids of the plasma; but it has also been suggested that the association is one with sodium as sodium bicarbonate, and further that the hæmoglobin of the corpuscles plays a part in promoting the dissociation of the sodium bicarbonate or even the carbonate, and thus keeping up the carbonic acid of the entire blood. Other observers however maintain that the plasma does not hold this exclusive possession of the carbonic acid, but that a considerable quantity of this gas is in some way associated with the red corpuscles. Indeed further investigations are necessary before the matter can be said to have been placed on a satisfactory footing.

The relations of the Nitrogen in the Blood.

§ **353**. The small quantity of this gas which is present in both arterial and venous blood seems to exist in a state of simple solution.

SEC. 5. THE RESPIRATORY CHANGES IN THE LUNGS.

The Entrance of Oxygen.

§ **354**. We have already seen that the blood in passing through the lungs takes up a certain variable quantity (from 8 to 12 vols. p.c.) of oxygen. We have further seen that the quantity so taken up, putting aside the insignificant fraction simply absorbed, enters into direct but loose combination with the hæmoglobin. In drawing a distinction between the oxygen simply absorbed and that entering into combination with the hæmoglobin, it must not be understood that the latter is wholly independent of pressure. On the contrary, all chemical compounds are in various degrees subject to dissociation at certain pressures and temperatures; and the existence of the somewhat loose compound of oxygen and hæmoglobin is dependent on the partial pressure of oxygen in the atmosphere to which the hæmoglobin is exposed. Not only will a solution of hæmoglobin or a quantity of blood either absorb oxygen and thus undergo association or undergo dissociation and give off oxygen according as the partial pressure of oxygen in the atmosphere to which it is exposed is high or low, but also the amount taken up or given off will depend on the degree of the partial pressure; the hæmoglobin as we have seen may be partially as well as wholly reduced. The law however according to which absorption or escape thus takes place is quite different from that observed in the simple absorption of oxygen by liquids. The association or dissociation is further especially dependent on temperature, a high temperature favouring dissociation, so that at a high temperature less oxygen is taken up than would be taken up (or, as the case may be, more given off than would be given off) at a lower temperature, the partial pressure of the oxygen in the atmosphere remaining the same.

Moreover in the blood we have to deal not with hæmoglobin in simple solution, in which the molecules are dispersed uniformly through the solvent, but with the hæmoglobin segregated into minute isolated masses, bottled up as it were in the individual corpuscles. The hæmoglobin of each corpuscle is separated from its fellows by a layer, thin it may be but still a distinct layer, of colourless, hæmoglobinless plasma. As the corpuscle makes its way through the narrow capillary paths of a pulmonary alveolus, it is separated from the air of the alveolus by a thin layer of plasma as well as by the film of the conjoined capillary and alveolar walls; and a like layer of plasma separates it from its fellows as it journeys in company with them through the wider passages of the arteries and veins. Through this layer of plasma, which containing no hæmoglobin can hold oxygen in simple solution only, the oxygen has to pass on its way to and from the corpuscle; and every corpuscle may be considered as governing, as far as oxygen is concerned, a zone of plasma immediately surrounding itself. The corpuscle takes its oxygen directly from this zone and gives up its oxygen directly to this zone; and the pressure at which at any moment the oxygen exists in this zone will depend on the pressure of oxygen outside the zone, in the air of the pulmonary alveolus for instance, and on the smaller or greater amount of oxygen associated with the hæmoglobin of the corpuscle.

The film of the conjoined capillary and alveolar wall is a thin membrane soaked with lymph and wet; we cannot speak of it as actually secreting a liquid secretion into the alveolus, for the cavity of the alveolus is filled with air which, though saturated with moisture, is air, not a liquid; still enough passes through the film to keep it continually moist. Through this film the oxygen has to make its way in order to gain access to the plasma and so to the corpuscle; it makes its way dissolved in the fluid, that is the lymph, which keeps the film moist. This film moreover is composed of living matter, and the considerations which a little while back (§ 312) we urged concerning the diffusion through a living membrane of solid substances in solution, hold good also for the diffusion of gases in solution.

We have now to consider the question, Are the conditions in which hæmoglobin and oxygen exist in ordinary venous blood as it flows to the lungs, of such a kind that the venous blood in passing through the pulmonary capillaries will find the partial pressure of the oxygen in the pulmonary alveoli sufficient to bring about the association of the additional quantity of oxygen whereby the venous is converted into arterial blood?

We may say at once that we have, at present at all events, no satisfactory evidence that the film spoken of above exerts any influence, as a living film, on the entrance of oxygen from the alveolus into the blood. Nor have we any evidence that as a mere membrane or septum it exerts any such influence; the oxygen appears to pass into the blood in the same way that it would, if the blood were freely exposed without any intervening partition to the alveolar air. Further, the evidence, so far as it goes, seems to shew that blood absorbs oxygen in the same way as an aqueous solution of hæmoglobin of the same concentration; the zone of plasma spoken of above as surrounding each corpuscle behaves as far as regards the passage of oxygen to and from the corpuscles in no essentially different respect from the way the molecules of water, belonging to a molecule of dissolved hæmoglobin, behave in regard to the absorption or the giving-off of oxygen by an aqueous solution of hæmoglobin.

§ **355**. In man, as we have seen, expired air contains about 16 p.c. of oxygen. The air in the pulmonary alveoli must contain less than this, since the expired air consists of tidal air mixed by diffusion with the stationary air. How much less it contains we do not exactly know, but probably the difference is not very great. At the ordinary atmospheric pressure of 760 mm. 16 p.c. is equivalent to a partial pressure of 122 mm. The question therefore stands thus, Will venous blood, exposed at the temperature of the body to a partial pressure of less than 122 mm. (less than 16 p.c.) of oxygen take up sufficient oxygen (from 8 to 12 vols. p.c.) to convert it into arterial blood? Numerous experiments have been made (chiefly but not exclusively on the dog) to determine on the one hand the oxygen-pressure of both arterial and venous blood (*i.e.* the partial pressure of oxygen in an atmosphere exposed to which the arterial blood neither gives up nor takes in oxygen, and the same for venous blood), and on the other hand the behaviour at the temperature of the body or at ordinary temperatures of blood or of solutions of hæmoglobin (for the two as we have just said behave in this respect very much alike) towards an atmosphere in which the partial pressure of oxygen is made to vary. Without going into detail, we may state that these experiments shew that the partial pressure of oxygen in the lungs is amply sufficient to bring about, at the temperature of the body, the association of that additional amount of oxygen by which venous blood becomes arterial. When a solution of hæmoglobin or when blood is successively exposed to increasing oxygen pressures, as the partial pressure of oxygen is gradually increased, the curve of absorption rises at first very rapidly but afterwards more slowly; that is to say, the later additions of oxygen at the higher pressures are proportionately less than the earlier ones at the lower pressures. And this is consonant with what appears to be the fact that the hæmoglobin of arterial blood though nearly saturated with oxygen, *i.e.* associated with almost its full complement of oxygen, is not quite saturated. When arterial blood is thoroughly exposed to air it takes up rather more than 1 vol. p.c. of oxygen; and that appears to represent the difference between exposing blood to pure air, such as enters or ought to enter the mouth in inspiration, and exposing blood to the air as it exists in the pulmonary alveoli. The greater relative absorption at the lower pressures has a beneficial effect in as much as it still permits a considerable quantity of oxygen to be absorbed even when the partial pressure of oxygen in the air in the lungs is largely reduced, as in ascending to great heights.

Observations made both with dog's blood and ox's blood seem to shew that arterial blood ceases to take up oxygen and begins to give off oxygen, in other words, that dissociation begins to take place, when the partial pressure of the oxygen in the atmosphere to which it is exposed sinks to about 60 mm. of mercury, that is to say, when the whole atmospheric pressure is reduced from 760 mm. to about 300 mm. or when the percentage of oxygen in the atmosphere is reduced by decidedly more than half. And this accords with the observation that, in man, when the oxygen of inspired air is gradually diminished, without any other change in the air, symptoms of dyspnœa do not make their appearance until the oxygen sinks to 10 p.c. in the inspired air and must therefore be less than this in the pulmonary alveoli. We may remark that at ordinary altitudes, even taking into account the diminution the oxygen undergoes before it reaches the pulmonary alveoli, the partial pressure of the oxygen in the atmosphere leaves a wide margin of safety. But at an altitude of 5500 metres (17000 feet) at which the pressure of the whole atmosphere stands at about the limit given above of 300 mm., the partial pressure of the oxygen will be such that the venous blood cannot take up the quantity of oxygen proper to convert it into arterial blood, since at this limit arterial blood begins to give off oxygen. We may add that it is at this altitude that breathing becomes especially difficult, but to this we shall return.

§ **356**. The statements made so far refer to ordinary breathing, but the question may be asked, What happens when the renewal of the air in the pulmonary alveoli ceases, as when the trachea is obstructed? In such a case the oxygen in the alveoli is found to diminish rapidly, so that the partial pressure of oxygen in them soon falls below the oxygen-pressure of ordinary venous blood. But in such a case the blood is no longer ordinary venous blood; instead of being moderately, it is largely and increasingly reduced; instead of containing a comparatively small amount, it contains a large and gradually increasing amount, of reduced hæmoglobin. And as the reduction continues to increase, the oxygen-pressure of the venous blood also continues to decrease; it thus keeps below that of the air in the lungs. Hence apparently even the last traces of oxygen in the lungs may be taken up by the blood, and carried away to the tissues.

The Exit of Carbonic Acid.

§ **357**. It seems natural to suppose that the carbonic acid would escape by diffusion from the blood of the alveolar capillaries into the air of the alveoli. But in order that diffusion should thus take place, the carbonic acid pressure of the air in the pulmonary alveoli must always be less than that of the venous blood of the pulmonary artery, and ought not to exceed that of the blood of the pulmonary vein. There are however many practical difficulties in the way of an exact determination of the carbonic acid pressure of the pulmonary alveoli (for though it must be greater than that of the expired air, it is difficult to say how much greater), and of the carbonic acid pressure of the blood at the same time, so as to be in a position to compare the one with the other. In the case of oxygen, there is always present in the lungs a surplus of the gas, a portion only being absorbed at each breath; in the case of carbonic acid, the whole quantity comes direct from the blood, and any modifications in breathing seriously affect the amount given out. Thus when the breath is held for some time the percentage of carbonic acid in the expired air reaches 7 or 8 p.c., but we cannot take this as a measure of the normal percentage of carbonic acid in the pulmonary alveoli, since by the mere holding of the breath the carbonic acid in the blood and hence in the pulmonary alveoli is increased beyond the normal.

The difficulties of the problem seem however to have been overcome by an ingenious experiment in which there is introduced into the bronchus of the lung of a dog a catheter, round which is arranged a small bag; by the inflation of this bag the bronchus, whenever desired, can be completely blocked up. Thus, without any marked disturbance of the general breathing, and therefore without any marked change in the normal proportions of the gases of the blood, the experimenter is able to stop the ingress of fresh air into a limited portion of the lung. At the same time he is enabled by means of the catheter to withdraw a sample of the air of the same limited portion, and by analysis to determine the amount of carbonic acid which it contains, or in other words, the partial pressure of the carbonic acid. The blood passing through the alveolar capillaries of this limited portion of the lung naturally possesses the same carbonic acid pressure as the rest of the venous blood flowing through the pulmonary artery, a pressure which, though varying slightly from moment to moment, will maintain a normal average. On the supposition that carbonic acid passes simply by diffusion from the pulmonary blood into the air of the alveoli, because the carbonic acid pressure of the latter is normally lower than that of the former, one would expect to find that the air in the occluded portion of the lung would continue to take up carbonic acid until an equilibrium was established between it and the carbonic acid pressure of the venous blood. Consequently, if after an occlusion, say of some minutes (by which time the equilibrium might fairly be assumed to have been established), the carbonic acid pressure of the air of the occluded portion were determined, it ought to be found to be equal to, and not more than equal to, the carbonic acid pressure of the venous blood of the pulmonary artery. And this is the result which has been arrived at; it has been found that the pressures of the carbonic acid of the occluded air and of the venous blood of the right side of the heart are just about equal. Hence the evidence so far as it goes is distinctly in favour of the view that the escape of carbonic acid from the blood into the pulmonary alveoli is simply due to diffusion, and that there is no need to seek for any further explanation. There is, as far as we can see at present at all events, no necessity, any more than in the case of oxygen, to suppose that the wall of the pulmonary alveoli has any specific secretory power of discharging carbonic acid from the blood independently of or in antagonism to the influence of pressures, or that it exerts any special influence at all as a diffusion septum.

There are some facts which seem to suggest that the exit of carbonic acid from the blood is assisted by the simultaneous entrance of oxygen, but this is not definitely proved. If such an aid is given, it is probably brought about by the change in the hæmoglobin in some indirect way raising the pressure of the carbonic acid in the blood.

As far then as can be seen at present, both the entrance of oxygen and the exit of carbonic acid by which venous blood is converted into arterial are the simple physical results of the exposure of the blood in the pulmonary capillary to the air of the pulmonary alveoli.

SEC. 6. THE RESPIRATORY CHANGES IN THE TISSUES.

§ **358**. In passing through the several tissues the arterial blood becomes once more venous. The oxyhæmoglobin becomes considerably reduced, and a quantity of carbonic acid passes from the tissues into the blood. The amount of change varies in the various tissues, and in the same tissue may vary at different times. Thus in a gland at rest, as we have seen, the venous blood is dark, shewing that the hæmoglobin is to a large extent in the reduced condition; when the gland is active, the venous blood in its colour, and in the extent to which the hæmoglobin is in the condition of oxyhæmoglobin, resembles closely arterial blood. The blood therefore which issues from a gland at rest is more 'venous' than that from an active gland; though owing to the more rapid flow of blood which, as we saw in an earlier section, accompanies the activity of the gland, the total quantity of oxygen taken up from and of carbonic acid discharged into the blood from the gland in a given time may be greater in the latter. The blood, on the other hand, which comes from an active, *i.e.* a contracting muscle, is, in spite of the more rapid flow, not only richer in carbonic acid, but also, though not to a corresponding amount, poorer in oxygen than the blood which flows from a muscle at rest.

In all these cases the great question which comes up for our consideration is this: Does the oxygen pass from the blood into the tissues, and does the oxidation take place in the tissues, giving rise to carbonic acid, which passes in turn away from the tissues into the blood? or do certain oxidizable reducing substances pass from the tissues into the blood, and there become oxidized into carbonic acid and other products, so that the chief oxidation takes place in the blood itself?

There are, it is true, reducing oxidizable substances in the blood, but these are small in amount, and the quantity of carbonic acid to which they give rise when the blood containing them is agitated with air or oxygen, is so small as scarcely to exceed the errors of observation.

On the other hand, it will be remembered that in speaking of muscle, we drew attention (§ 61) to the fact that a frog's muscle removed from the body (and the same is true of the muscles of other animals) contains no free oxygen whatever; none can be obtained from it by the mercurial air-pump. Yet such a muscle will not only when at rest go on producing and discharging a certain quantity, but also when it contracts evolve a very considerable quantity, of carbonic acid. Moreover this discharge of carbonic acid will go on for a certain time in muscles under circumstances in which it is impossible for them to obtain oxygen from without. Oxygen, it is true, is necessary for the life of the muscle: when venous instead of arterial blood is sent through the blood vessels of a muscle, the irritability speedily disappears, and unless fresh oxygen be administered the muscle soon dies. The muscle may however, during the interval in which irritability is still retained after the supply of oxygen has been cut off, continue to contract vigorously. The supply of oxygen, though necessary for the *maintenance* of irritability, is not necessary for the *manifestation* of that irritability, is not necessary for that explosive decomposition which developes a contraction. A frog's muscle will continue to contract and to produce carbonic acid in an atmosphere of hydrogen or nitrogen, that is, in the total absence of free oxygen both from itself and from the medium in which it is placed.

Thus on the one hand the muscle seems to have the property of taking up and fixing in some way or other the oxygen to which it is exposed, of storing it up in its own substance in such a condition that it cannot be removed by simple diminished pressure (so that the pressure of oxygen in the muscular substance may be considered as always nil), and yet has not entered into any distinct combination which we can speak of as an oxidation, but is still available for such a purpose. The idea has been put forward that the oxygen in this condition is physically attached to and lies between the molecules of the muscular substance without being chemically combined with them, and hence has been spoken of as "intra-molecular" oxygen; but we have no exact knowledge as to what its condition really is at this stage. On the other hand the muscular substance is always undergoing a decomposition of such a kind that carbonic acid is set free, sometimes, as when the muscle is at rest, in small, sometimes, as during a contraction, in large quantities. The oxygen present in this carbonic acid, as an oxidation product, comes from the previously existing store of which we have just spoken. The oxygen taken in by the muscle, whatever be its exact condition immediately upon its entrance into the muscular substance, in the phase which has been called 'intra-molecular,' sooner or later enters into a combination, or perhaps we should rather say, enters into a series of combinations. We have previously urged (§ 30) that all living substance may be regarded as incessantly undergoing changes of a double kind, changes of building up and changes of breaking down. In the end-products of the breaking down, in the carbonic acid given out by muscle for instance, we can recognize an oxidation product; but we do not know exactly at what stage or exactly in what way the oxygen is combined with the carbon. We may imagine that the oxygen, as it comes from the blood, is caught up so to speak by, and disappears in, the building up processes (forming, possibly at the very beginning, with some constituent of the muscular substance a combination like to but firmer and more stable than its combination with hæmoglobin) and that through those processes it is made part of complex decomposable substances whose decomposition ultimately gives rise to the carbonic acid; but, as far as actual knowledge goes, we cannot as yet trace out the steps taken by the oxygen from the moment it slips from the blood into the muscular substance to the moment when it issues united with carbon as carbonic acid. The whole mystery of life lies hidden in the story of that progress, and for the present we must be content with simply knowing the beginning and the end.

But if the oxygen-pressure of the muscular tissue be thus always nil, oxygen will be always passing over from the blood-corpuscles, in which it is at a comparatively high pressure, through the plasma, through the capillary walls, the lymph-spaces and the sarcolemma, into the muscular substance, and as soon as it arrives there will be in some manner or other hidden away, leaving the oxygen-pressure of the muscular substance once more nil. Conversely, the carbonic acid produced by the decomposition of the muscular substance will tend to raise the carbonic acid pressure of the muscle until it exceeds that of the blood; whereupon carbonic acid will pass from the muscle into the blood, its place in the muscular substance being supplied by freshly generated supplies. There will always in fact be a stream of oxygen from the blood to the muscle and of carbonic acid from the muscle to the blood. The respiration of the muscle then does not consist in throwing into the blood oxidizable substances, there to be oxidized into carbonic acid and other matters; but it does consist in the assumption and storing up of oxygen somehow or other in its substance, in the building up by help of that oxygen of explosive decomposable substances, and in the carrying out of decompositions whereby carbonic acid and other matters are discharged first into the substance of the muscle and subsequently into the blood.

§ **359**. Our knowledge of the respiratory changes in muscle is more complete than in the case of any other tissue; but we have no reason to suppose that the phenomena of muscle are exceptional. On the contrary, all the available evidence goes to shew that in all tissues the oxidation takes place in the tissue, and not in the adjoining blood. It is a remarkable fact, that lymph, serous fluids, bile, urine, and milk contain a mere trace of free or loosely combined oxygen, but a very considerable quantity of carbonic acid. And we may probably assert with safety with regard to all the tissues that in the tissues themselves, in the lymph which bathes their lymph-spaces, and in the secretions which some of them pour forth free oxygen is either wholly absent or so scanty that their oxygen-pressure may be regarded as nil, while carbonic acid is so abundant that the pressure of carbonic acid in them may be regarded as exceeding that of venous blood. An exception seems to be presented by the case of the lymph flowing along the larger lymphatic vessels, for in this the amount of carbonic acid, while usually higher than that of arterial blood, is lower than that of the general venous blood; but this probably is due to the fact that the lymph in its passage onwards is largely exposed to arterial blood in the connective tissues and in the lymphatic glands, where the production of carbonic acid is slight as compared to that going on in muscles. All the facts point to the conclusion, that it is the tissues, and not the blood, which become primarily loaded with carbonic acid, the latter simply receiving the gas from the former by diffusion, except the (probably) small quantity which results from the metabolism of the blood-corpuscles; and that the oxygen which passes from the blood into the tissues is at once taken up and placed under such conditions that it is no longer removable by diminished pressure.

In further support of this view may be urged the fact that if, in a frog, the whole blood of the body be replaced by normal saline solution, the total metabolism of the body is, for some time, unchanged. The saline medium is able owing to the low rate of metabolism, and large (cutaneous) respiratory surface of the animal, to supply the tissues with all the oxygen they need, and to remove all the carbonic acid they produce. It is difficult to believe that, in such an experiment, the oxidation took place in the saline solution itself while circulating in the blood vessels and tissue-spaces of the animal.

We may add, that the oxidative power which the blood itself removed from the body is able to exert on substances which are undoubtedly oxidized in the body is so small that it may be neglected in the present considerations. If grape-sugar be added to blood, or to a solution of hæmoglobin, the mixture may be kept for a long time at the temperature of the body, without undergoing oxidation. Even within the body a slight excess of sugar in the blood over a certain percentage wholly escapes oxidation, and is discharged unchanged. Many easily oxidized substances, such as pyrogallic acid, pass largely through the blood of a living body and are discharged in the urine without being oxidized; though perhaps in some of these cases, what appears to be an absence of oxidation is really an oxidation followed by a subsequent equivalent reduction taking place in the urine or elsewhere. The organic acids, such as citric, even in combination with alkaline bases, are only partially oxidized; when administered as acids, and not as salts, they are hardly oxidized at all. It is of course quite possible that the changes which the blood undergoes when shed might interfere with its oxidative action, and hence the fact that shed blood has little or no oxidizing power, is not a satisfactory proof that the unchanged blood within the living vessels may not have such a power. But did oxidation take place largely in the blood itself, one would expect even highly diffusible substances to be oxidized in their transit; whereas if we suppose the oxidation to take place in the tissues, it becomes intelligible why such diffusible substances as those which the tissues in general refuse to take up largely, should readily pass unchanged from the blood through the excreting organs.

We have seen that in muscle the production of carbonic acid is not directly dependent on the consumption of oxygen. The muscle produces carbonic acid in an atmosphere of hydrogen. What is true of muscle is true also of other tissues and of the body at large. It was shewn long ago that animals might continue to breathe out carbonic acid in an atmosphere of nitrogen or hydrogen; and this has more recently been illustrated by the remarkable experiment, that a frog kept at a low temperature will live for several hours, and continue to produce carbonic acid, in an atmosphere absolutely free from oxygen. The carbonic acid produced during this period was made by help of the oxygen inspired in the hours anterior to the commencement of the experiment. The oxygen then absorbed was stowed away from the hæmoglobin into the tissues, it was made use of to build up the explosive compounds, whose explosions later on gave rise to the carbonic acid. Or, to adopt a simile which has been suggested, the oxygen helps to wind up the vital clock; but once wound up the clock will go on for a period without further winding. The frog will continue to live, to move, to produce carbonic acid for a while without any fresh oxygen, as we know of old it will without any fresh food; it will continue to do so till the explosive compounds which the oxygen built up are exhausted; it will go on till the vital clock has run down.

§ **360**. To sum up, then, the results of respiration in its chemical aspects. As the blood passes through the lungs, the low oxygen pressure of the venous blood permits the entrance of oxygen from the air of the pulmonary alveolus, through the thin alveolar wall, through the thin capillary sheath, through the thin layer of blood-plasma, to the red corpuscle, and the reduced hæmoglobin of the venous blood becomes wholly, or all but wholly, oxyhæmoglobin. Hurried to the tissues, the oxygen, at *comparatively* high pressure in the arterial blood, passes largely into them. In the tissues, the oxygen-pressure is always kept at an exceedingly low pitch, by the fact that they, in some way at present unknown to us, pack away at every moment into some stable combination each molecule of oxygen which they receive from the blood. With its oxyhæmoglobin largely but not wholly reduced, the blood passes on as venous blood. To what extent the hæmoglobin is reduced will depend on the activity of the tissue itself. The quantity of hæmoglobin in the blood is the measure of limit of the oxidizing power of the body at large; but within that limit the amount of oxidation is determined by the tissue, and by the tissue alone.

We cannot trace the oxygen through its sojourn in the tissue. We only know that sooner or later it comes back combined in carbonic acid (and other matters not now under consideration). Owing to the continual production of carbonic acid, the pressure of that gas in the extravascular elements of the tissue is always higher than that in the blood; the gas accordingly passes from the tissue into the blood, and the venous blood passes on not only with its hæmoglobin more or less reduced, *i.e.* with its oxygen-pressure decreased, but also with its carbonic acid pressure increased. Arrived at the lungs, the blood finds the pulmonary air at a lower carbonic acid pressure than itself. The gas accordingly streams through the thin vascular and alveolar walls until the pressure without the blood vessel is equal to the pressure within. At the same time the blood finds in the air of the pulmonary alveoli a supply of oxygen, more than adequate to convert, not entirely but nearly so, the reduced hæmoglobin back again to oxyhæmoglobin. Thus the air of the pulmonary alveoli, having given up oxygen to the blood and taken up carbonic acid from the blood, having in consequence a higher carbonic acid pressure and a lower oxygen pressure than the tidal air in the bronchial passages, mixes rapidly with this by diffusion. The mixture is further assisted by ascending and descending currents; and the tidal air issues from the chest at the breathing out poorer in oxygen and richer in carbonic acid than the tidal air which entered at the breathing in.

SEC. 7. THE NERVOUS MECHANISM OF RESPIRATION.

§ **361**. Breathing is an involuntary act. Though the diaphragm and all the other muscles employed in respiration are voluntary muscles, *i.e.* muscles which can be called into action by a direct effort of the will, and though respiration may be modified within very wide limits by the will, yet we habitually breathe without the intervention of the will: the normal breathing may continue, not only in the absence of consciousness, but even after the removal of all the parts of the brain above the medulla oblongata.

We have already seen how complicated is even a simple respiratory act. A very large number of muscles are called into play. Many of these are very far apart from each other, such as the diaphragm and the nasal muscles; yet they act in harmonious sequence in point of time. If the lower intercostal muscles contracted before the scaleni, or if the diaphragm contracted alternately with the other chest-muscles, the satisfactory entrance and exit of air would be impossible. These muscles moreover are coordinated also in respect of the amount of their several contractions; a gentle and ordinary contraction of the diaphragm is accompanied by gentle and ordinary contractions of the intercostals, and these are preceded by gentle and ordinary contractions of the scaleni. A forcible contraction of the scaleni, followed by simply a gentle contraction of the intercostals, would perhaps hinder rather than assist inspiration, and at all events would be waste of power. Further, the whole complex inspiratory effort is often followed by a less marked but still complex expiratory action. It is impossible that all these so carefully coordinated muscular contractions should be brought about in any other way than by coordinate nervous impulses descending along efferent nerves from a coordinating nervous centre. By experiment we find this to be the case.

When in a rabbit the trunk of a phrenic nerve is cut, the diaphragm on that side remains motionless, and respiration goes on without it. When both nerves are cut, the whole diaphragm remains quiescent, though the costal respiration becomes excessively laboured.

When an intercostal nerve is cut, no active respiratory movements are seen in the intercostal muscles of the corresponding space, and when the spinal cord is divided below the origin of the seventh cervical spinal nerve, that is below the exits of the roots of the phrenic nerves, costal respiration ceases, though the diaphragm continues to act, and that with increased vigour. When the cord is divided just below the medulla, all thoracic movements cease, but the respiratory actions of the nostrils and glottis still continue. These however disappear when the facial and recurrent laryngeal nerves are divided. We have already stated that after removal of the brain above the medulla, respiration still continues very much as usual, the modifications which ensue from the loss of the brain being unessential. Hence, putting all these facts together, it is clear that the respiratory movements are, as we suggested, brought about by coordinated impulses which, developed in the central nervous system and starting in the first instance in the medulla, find their way along the several efferent nerves. The proof is completed by the fact that the removal of or extensive injury to the medulla alone is, save in exceptional cases which we will discuss presently, at once followed by the cessation of all respiratory movements, even though the rest of the nervous system including every muscle and every nerve concerned be left intact. Nay more, if only a small portion of the medulla, a tract whose limits have not been clearly defined, but which may be described as lying below the vaso-motor centre in the immediate neighbourhood of the nuclei of the vagus nerves, be removed or injured, respiration ceases, and death at once ensues. Hence this portion of the nervous system was called by Flourens the vital knot, or ganglion of life, '*nœud vital.*' We shall speak of it as the *respiratory centre.*

§ **362**. The nature of this centre must be exceedingly complex; for while even in ordinary respiration it gives rise to a whole group of coordinate nervous impulses of inspiration followed in due sequence by a smaller but still coordinate group of expiratory impulses of an antagonistic nature, in laboured respiration fresh and larger impulses are generated, though still in coordination with the normal ones, the expiratory events being especially augmented; and in the cases of more extreme dyspnœa and asphyxia impulses overflow, so to speak, from it in all directions, though only gradually losing their coordination, until almost every muscle in the body is thrown into contractions.

We must not however conceive of this centre as one of such a kind that the impulses leave it fully coordinated and equipped so that nothing remains for them but to travel, unchanged, along the several efferent nerve-fibres to their several muscular destinations. On the contrary we have reason to think that the respiratory motor nerves, like other motor nerves, are connected, just as they are about to issue from the spinal cord, with a nervous machinery, in which nerve cells play a part—a point which we shall consider more fully in treating of the spinal cord; we have reason to think that the respiratory impulses starting from the respiratory centre pass into and are modified by secondary spinal nervous mechanisms before they issue along the motor nerve-roots. Indeed observations shew that under particular conditions, and especially in young animals, respiratory movements may be carried out in the entire absence of the medulla oblongata. Thus if in a kitten or puppy, or young rabbit, after division of the spinal cord below the medulla, artificial respiration be kept up, and then pauses be made in the artificial respiration, during these pauses not only may what appear to be respiratory movements be induced, in a reflex manner, by pinching or by blowing on the skin, but, especially if the excitability of the spinal cord be heightened by small doses of strychnia, even spontaneous efforts of breathing may occasionally be observed. These are the exceptional instances mentioned above. Since in such cases the rhythmically repeated movements of the respiratory muscles are sometimes accompanied by rhythmic movements of the fore and hind limbs not respiratory in nature, it may be doubted whether these experiments really prove the existence of distinct respiratory centres in the spinal cord; and at most they merely shew that the respiratory nervous mechanism is not entirely confined, as was once thought, to the centre in the medulla, but also embraces other subsidiary mechanisms, which may perhaps be spoken of as centres, in the spinal cord below. It has indeed been maintained by some that these lower spinal centres are the chief centres and that the medullary centre acts merely in the way of regulating these; but it is difficult to reconcile this view with the experience that interference with the medulla, limited entirely to the medulla, so often leads to the entire abolition of the respiratory movements. The matter is not at present thoroughly worked out, but we shall probably not greatly err in regarding the respiratory nervous system as in many ways analogous to the vaso-motor nervous system, with its head centre in the medulla, and secondary centres elsewhere, and in continuing to speak of the centre in the medulla as being "the respiratory centre" while admitting that it works through other nervous machinery placed lower down in the spinal cord, and that this subordinate machinery may, in exceptional cases, carry out, though inadequately, the work of the chief centre.

§ **363**. Admitting then the existence of this medullary respiratory centre the question naturally arises, Are we to regard its rhythmic action as due essentially to changes taking place in itself, or as due to afferent nervous impulses or other stimuli which affect it in a rhythmic manner from without? In other words, Is the action of the centre automatic or purely reflex? We know that the centre may be influenced by impulses proceeding from without, and that the breathing may be affected by the action of the will, or by an emotion, or by a dash of cold water on the skin, or in a hundred other ways; but the fact that the action of the centre may be thus modified from without, is no proof that the continuance of its activity is dependent on extrinsic causes.

In attempting to decide this question we naturally turn to the pneumogastric as being the nerve most likely to serve as the channel of afferent impulses setting in action the respiratory centre. If both vagus nerves be divided, respiration still continues, though in a modified form. This proves distinctly that afferent impulses ascending those nerves are not the efficient cause of the respiratory movements. We have seen that when the spinal cord is divided below the medulla, the facial and laryngeal movements still continue. This proves that the respiratory centre is still in action, though its activity is unable to manifest itself in any thoracic movement. But when the cord is thus divided, the respiratory centre is cut off from all sensory impulses, save those which may pass into it from the cranial nerves of sensory function; and that these sensory cranial nerves are not specially concerned in developing the activity of the respiratory centre is shewn by the fact that the division of these cranial nerves by themselves, when the medulla and spinal cord are left intact, does not do away with the continuance of respiration. One cranial nerve, as we shall see, is especially concerned in respiration, viz. the vagus nerve; but if after removal of the brain above the medulla both vagus nerves be divided, respiration still goes on; indeed the respiratory impulses proceeding from the centre are, though in a peculiar way, exaggerated. Hence though we cannot put the matter to an experimental test by dividing every sensory nerve in the body, while leaving the motor nerves of respiration intact, such an operation being practically impossible, we may infer that the respiratory impulses proceeding from the respiratory centre are not simply afferent impulses reaching the centre along afferent nerves and transformed by reflex action in that centre. They evidently start *de novo* from the centre itself, however much their characters may be affected by afferent impulses, reaching that centre at the time of their being generated. The action of the centre is automatic, not simply reflex.

§ **364**. We find, on inquiry, that the activity of the centre is profoundly influenced by two classes of events. These, as we might expect, are on the one hand events producing changes in the quality of the blood distributed to the medulla by the left ventricle, especially as regards its gases, that is to say, events modifying the interchange taking place in the lungs; and on the other hand nervous impulses, started in various ways and reaching the centre along various nerves or nervous tracts. It will be convenient to consider the latter first.

Afferent nervous impulses may affect the centre in many various ways. The whole act of breathing or of taking a breath is a double act consisting of an inspiration and an expiration, and nervous impulses may especially affect the one or the other. One mode of breathing may differ from another in the depth of the individual breath, in the volume of air taken in and given out; and nervous impulses may increase or may diminish the depth of a breath, the volume of air respired. One mode of breathing again differs from another in the rapidity with which one breath succeeds another, that is, in the rate of rhythm; and nervous impulses may slow or may quicken the rate of rhythm. Then, again, combinations of effects so numerous and varied as almost to baffle description may result from the influence of various nervous impulses. Emotions may affect a single breath or a long series of breaths, may quicken the rhythm while making each breath more shallow or may at the same time make each breath deeper, or may slow the rhythm in either the one or the other manner, and may bear chiefly on inspiration or on expiration. Moreover there is not an afferent nerve in the body which by means of afferent impulses passing along it, may not be the instrument of influencing the respiratory centre. Of all the automatic centres in the body the respiratory centre is the one whose independence is most obscured by the repeated effects of afferent nervous impulses.

Certain afferent nerves however appear to be more closely connected with it than others; and of these the most conspicuous and important are the two vagus nerves, which we have already mentioned in this connection. Their importance is well illustrated by the following experiments. If one vagus be divided in an ordinary way, without any special precautions, the respiration is

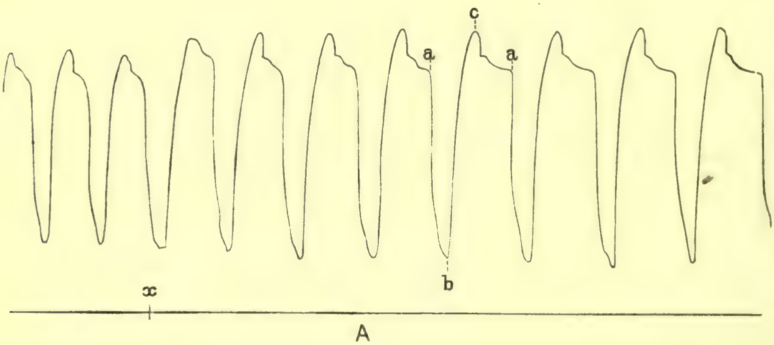

Fig. 77. Effect on Respiration of section of one Vagus.

The vagus was divided at the point marked x. The curve was obtained by means of a tambour connected with a receiver into which the animal (rabbit) breathed as shewn in Fig. 71, the lever falling in inspiration as air is sucked out of the tambour, and rising in expiration as the air returns. Inspiration begins at a and ends at b. Expiration begins at b and ends at c. The lever gradually falls between c and a owing to the escape of air from the apparatus.

either not materally changed, or if affected becomes slower (Fig. 77). If both be divided (Fig. 78) it becomes very slow, the pauses between expiration and inspiration being markedly prolonged. The character of the respiratory movement too is markedly changed; each respiration is fuller and deeper, so much so indeed that, according to some observers, what is lost in rate is gained in extent, the amount of carbonic acid produced and oxygen consumed in a given period remaining after division of the nerves about the same as when these were intact; but it is undesirable to insist too much on the exactness of this compensation.

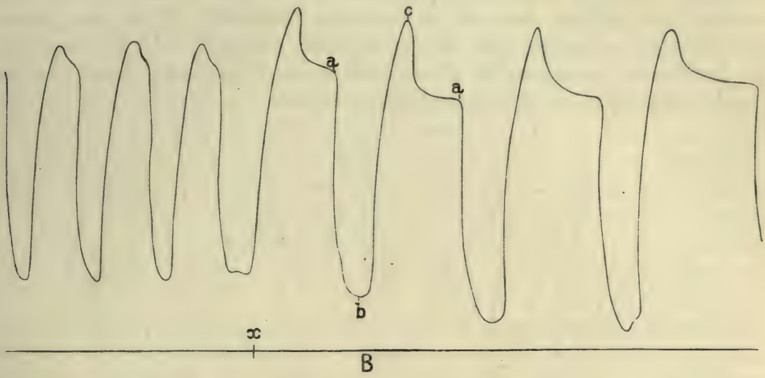

FIG. 78. EFFECT ON RESPIRATION OF SECTION OF BOTH VAGUS NERVES.

The curve was obtained in the same way as Fig. 77. The second vagus nerve was divided at *x*.

When after division of both vagus nerves in the neck, the medulla being intact, the central stump, that connected with the central nervous system, of one of them is stimulated with a gentle interrupted current, the effects are not always the same; one

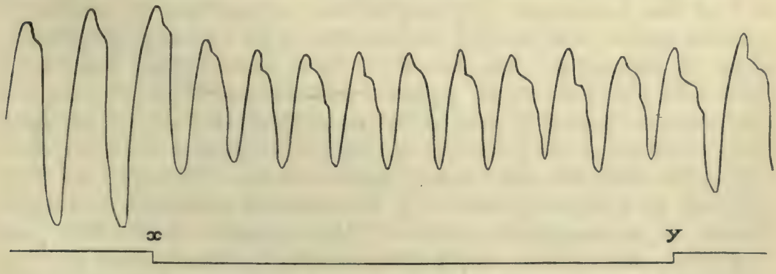

FIG. 79. QUICKENING OF RESPIRATION BY GENTLE STIMULATION OF THE CENTRAL END OF THE VAGUS TRUNK.

The curve was obtained in the same way as Figs. 77, 78. Stimulation of the vagus began at *x*, and ended at *y*.

of two results may follow and that whichever of the two nerves be used. In a certain number of cases, and these may perhaps be regarded as the more typical ones, the respiration, which from the division of the nerves had become slow, is quickened again (Fig. 79); and with care, by a proper application of the stimulus, the normal respiratory rhythm may for a time be restored. Upon the cessation of the stimulus, the slower rhythm returns. If the current be increased in strength, the rhythm may in some cases be so accelerated that inspiration begins before the expiration of the preceding breath is completed, Fig. 80; and this may go on until at last the diaphragm is brought into a condition of prolonged tetanus, and a standstill of respiration in an extreme inspiratory phase is the result. On the other hand in a certain number of cases the result is of an opposite character. Even though the respiration be already slowed by division of the nerves, stimulation produces a still further slowing, the pauses between each expiration and the succeeding inspiration are prolonged (cf. Fig. 81), and in a certain number of cases, actual standstill is brought about, but a standstill of a kind the opposite of the one just described, since the diaphragm which in that case was in prolonged tetanus is, in this case, completely relaxed, and remains for some time in the condition in which it is at the close of an ordinary breath. In a certain number of cases, and these are not uncommon, the result is intermediate between the two above

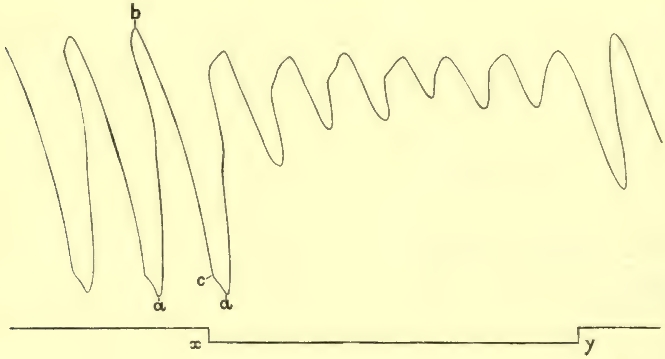

Fig. 80. Stimulation of Vagus leading to Inspiratory increase.

This curve, unlike the preceding, was obtained by inserting a needle through the body wall so as to rest on the diaphragm and attaching a lever to the needle; see § 328. The lever rises with each contraction of the diaphragm so that inspiration begins at *a* and ends at *b*, expiration begins at *b* and ends at *c*, the interval between *c* and *a* corresponding to the pause.

Stimulation of the vagus begins at *x*. It will be seen that upon stimulation the inspiratory rises of the lever begin long before the preceding expirations are complete.

extremes; the diaphragm stands still in a prolonged contraction in a position which is intermediate between the height of inspiration and expiration.

These results suggest the conclusion that the vagus nerve (we are dealing now with the main trunk of the nerve) contains afferent fibres of two kinds connected with the respiratory centre: one kind augmenting the action of the centre somewhat in the same way as the augmentor cardiac fibres augment the beat of the heart, and the other kind having an inhibitory effect. Apparently sometimes the one and sometimes the other kind is, according to circumstances, most provoked by the stimulation, much as in the same way as stimulation of the vagus in the frog, which as we have seen, § 158, is the channel for both inhibitory and augmentor cardiac impulses, produces, sometimes inhibition, sometimes augmentation of the heart beat. To affect the heart of course the stimulation of the vagus must be centrifugal, directed towards the periphery, whereas to affect the respiration it must be centripetal, applied to the part of the nerve connected with the brain; and while the usual effect on the heart of ordinary stimulation of the vagus is inhibition, augmentation only occurring in special cases, the most common effect on respiration is augmentation, though inhibition is not unfrequently seen. When the experiment is conducted on an animal under the full influence of chloral stimulation of the vagus generally produces inhibition of respiration, probably because the chloral renders the respiratory centre more susceptible to inhibitory influences.

§ **365**. We said just now "the action of the centre"; but the respiratory centre is a double one; it gives rise to inspiratory and to expiratory efferent impulses, and these are antagonistic the one to the other. If inspiratory and expiratory impulses issued from the centre at the same time and in equal potency, there could be no breathing at all, they would neutralize each other's effects; and indeed any amount of inspiratory impulse is antagonistic to a simultaneous expiratory impulse, and vice versa. Hence for the adequate services of the respiratory centre we might expect to find that each kind of afferent impulse ascending the vagus affected the centre in a double and opposite way, inhibiting expiration while augmenting inspiration, or inhibiting inspiration while augmenting expiration. If we allow ourselves to speak of the whole respiratory centre as consisting of two parts, one the inspiratory part, or inspiratory centre concerned in the issue of inspiratory impulses, and the other the expiratory part, or expiratory centre concerned in the issue of expiratory impulses, we may suppose that these centres are so related to each other that afferent impulses, reaching the medulla, which augment or inhibit the one, necessarily inhibit or augment the other. We need perhaps hardly add that of these two centres we should expect to find the inspiratory centre the dominant and the most responsive one; in normal breathing it comes almost alone into obvious use, since as we have seen the expiratory muscles have then a very slight task only, the chest being emptied chiefly by elastic reaction; and, speaking generally, breathing in is the first consideration, we breathe out mostly because we have already breathed in.

There are many facts which support this view of the double antagonistic action of afferent respiratory impulses. If the central end of the superior laryngeal branch of the vagus be stimulated the effects are much more constant than those of stimulating the main vagus trunk. Whether the main trunk of the nerve be previously severed or not, the result of centripetal stimulation of the superior laryngeal branch is always in the direction of a slowing of the respiration (Fig. 81); and this may by proper stimulation be carried so far that a complete standstill of respiration in the phase of rest is brought about. While the main trunk of the vagus contains fibres of two kinds, both augmentor and inhibitory of inspiration, the superior laryngeal branch appears to contain one kind only, those which inhibit inspiration. If now while this experiment is being conducted on a rabbit the abdomen be watched it will be seen that the inhibition of inspiration is accompanied by a contraction of the abdominal muscles, that is by an effort at expiration; the stimulation of the nerve while inhibiting respiration provokes, to a certain extent, expiration.

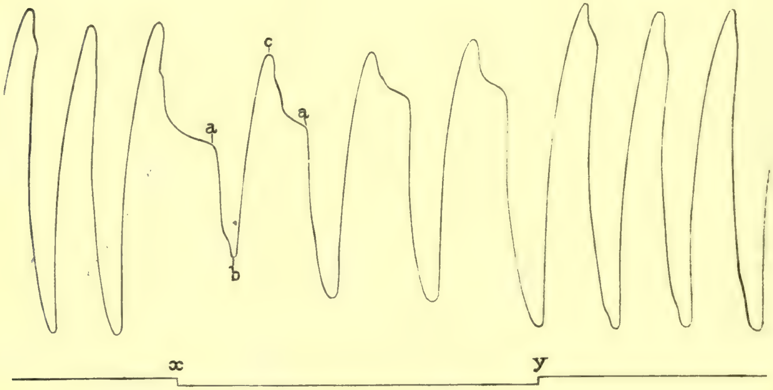

Fig. 81. Slowing of Respiration by stimulation of superior Laryngeal nerve.

This curve was obtained in the same way as Figs. 77, 8, 9 and the letters have the same meaning as in those figures. Stimulation begins at x, and ends at y.

§ 366. That the trunk of the vagus is the channel of these two kinds of impulses, of a mutually antagonistic character, is further shewn by applying what may be considered as natural stimuli to the endings of the nerve in the lungs; and the results so obtained have an especial value since the artificial stimulation of a nerve fibre at a part of its course by means of an electric current is at best a rough process, by which we cannot hope to do more than approximate to the results actually taking place in the living body when the nerve is stimulated at its endings by natural stimuli; and the approximation is perhaps less in the case of the exquisitely sensitive respiratory centre than in many other cases.

If in an animal in which a careful graphic record of the respiratory movements is being taken, the trachea be suddenly closed at the summit of an inspiration, the result is a pause before the succeeding inspiration follows, that is to say, a partial or temporary inhibition of inspiration; and if during such an experiment on a rabbit a curve be taken by means of the isolated slip of the diaphragm, § 328, it will be seen (Fig. 82 A) that the slip elongates somewhat; that is to say, previously in a state of slight tonic contraction, it changes in the direction of expiration. If on

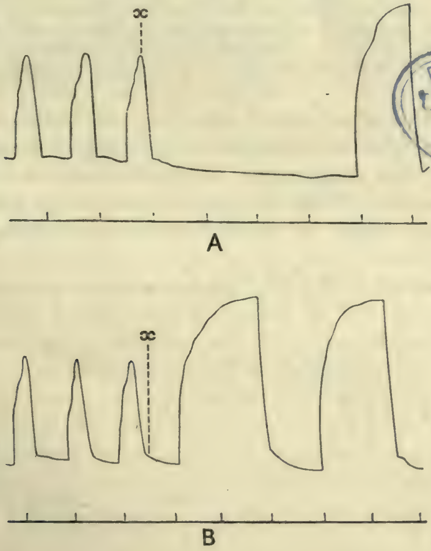

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FIG. 82. EFFECTS OF DISTENSION AND COLLAPSE OF LUNG. (Head.)

Both curves are described by a lever attached, as stated in § 328, to a slip of the diaphragm of a rabbit. A contraction of the diaphragm (inspiration) raises the lever; during relaxation of the diaphragm, the lever falls.

In A, the trachea is closed at x, the height of inspiration; a pause follows during which the lever gradually sinks until an inspiration (a very powerful one) sets in.

In B, the trachea is closed at the end of expiration, x; there follow powerful inspirations.

the other hand the trachea be suddenly closed at the end of an expiration (Fig. 82 B), when the lungs have returned to their emptied condition, the result is an increase of the sequent inspirations, that is to say, an augmentation of inspiratory impulses. If the chest or if the lung only be gently inflated a temporary cessation of all inspiration may be produced, accompanied sometimes by an attempt at expiration. If on the other hand air be sucked out of the chest, or if one lung be made to collapse by puncture of one pleural chamber, a prolonged inspiration is the frequent result, the diaphragm being thrown into a prolonged inspiratory tetanus. If the lungs are repeatedly inflated, without any means being taken to draw out the air after each inflation

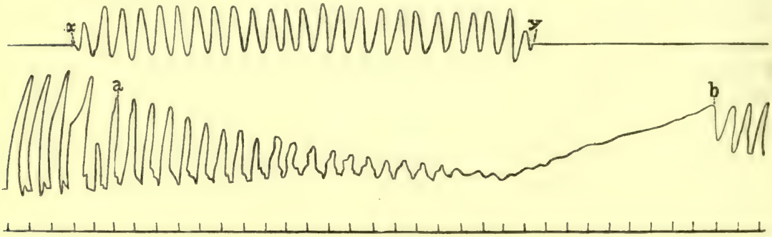

Fig. 83. Effects of repeated Inflations. Positive ventilation. (Head.)

The lower curve is described, as in Fig. 82, by a lever attached to a slip of the diaphragm. The upper curve shews the inflations from x to y, which were made without any attempt to draw the air out at each inflation; each rise on this curve denotes an inflation. It will be observed that as the inflations are continued the respiratory movements of the diaphragm are gradually "knocked down."

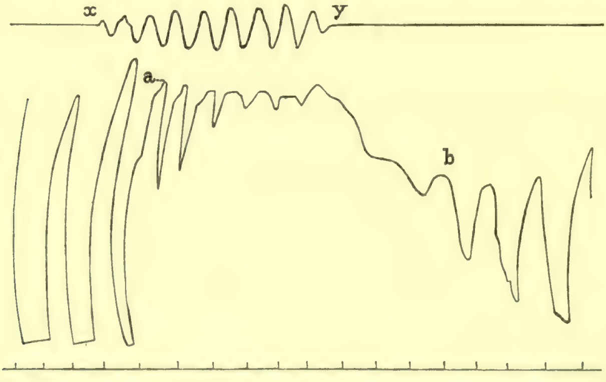

Fig. 84. Effects of repeated Suctions of the Lungs. Negative ventilation. (Head.)

The curve corresponds exactly to Fig. 83, except that the lungs are subjected to repeated suctions without corresponding inflations. The result is that the inspirations are repeated in such a way as to lead almost to an inspiratory tetanus of the diaphragm.

(Fig. 83), a procedure which we may speak of as positive ventilation, the result is that the inspiratory efforts are diminished, and if the ventilation is continued may cease altogether. If on the other hand air is repeatedly sucked out of the lungs, without any corresponding inflations, negative ventilation, the inspiratory efforts are increased (Fig. 84) and the increase may be such as to bring the diaphragm to a state of tetanus. And in general, though several complications occur which we cannot discuss here, the results of inflation of the lungs on the one hand and of suction or collapse of the lungs on the other hand, shew that the mere inflation or perhaps rather the mere distension of the lung tends to inhibit inspiratory and usher in expiratory impulses, while collapse of the lung tends to inhibit expiratory and to develope inspiratory impulses, the effect on the inspiratory impulses, as might be expected from the dominance of the inspiratory portion of the centre, being more marked than the effect on the expiratory impulses. That the instrument by which these effects are produced is the vagus nerve is shewn by the fact that they are no longer distinctly recognizable when both vagus nerves are divided. And that the results are due to the mere mechanical expansion and collapse of the lung in insufflation and collapse, and not to any chemical influences exerted by the larger amount or smaller amount of air present in the lung in the two cases increasing or diminishing the absorption of oxygen and escape of carbonic acid, is shewn by the fact that the results remain in their main features the same when some indifferent gas such as hydrogen is used for inflation instead of air or oxygen. We infer therefore that the expansion of the pulmonary alveoli in some way or other so stimulates the endings in the lung of the pulmonary branches of the vagus, that impulses are generated which ascending the vagus trunk inhibit the inspiratory processes in the respiratory centre; and that conversely collapse of the lung similarly generates impulses which are augmentative of inspiratory impulses. And, assuming on the strength of analogy the existence in the vagus of two sets of fibres we may say that expansion stimulates the endings of the fibres which inhibit inspiration and concurrently tend to augment expiration, while collapse stimulates the fibres which inhibit expiration and augment inspiration. The respiratory pump may thus be looked upon as a self-regulating mechanism: the expansion of the lungs which is the result of the efferent inspiratory impulses tends to check the issue of these impulses and to inaugurate the sequent expiration; and the return of the lungs in expiration tends to set going the succeeding inspiration.

The regulative influence exerted by impulses normally ascending the vagus nerves is further shewn by the following striking experiment. As we have already seen the brain above the medulla may be removed without any extraordinary change in the respiration taking place. We have also seen that when both vagus nerves are divided the respiration is slower and deeper, but is otherwise regular. If however after removal of the brain above the medulla both vagus nerves are divided, if the respiratory centre be cut off at one and the same time from impulses passing down from the higher parts of the brain, and from impulses ascending the vagus nerves, the result is that the respirations take on the form of a series of long continued inspiratory spasms. It would seem as if there were a tendency in the respiratory centre to go off into tetanic inspiratory explosions, that this tendency is held in check by impulses from the brain when the vagus nerves are divided, and by impulses along the vagus nerves when the brain is removed, but meets with no adequate checks when impulses from both sources are cut off at the same time.

§ 367. Hypotheses have been put forward to explain the changes in the respiratory centre which lead to the rhythmic discharge of inspiratory and expiratory impulses, and the further changes which result from the advent of augmenting and inhibitory impulses; but these as yet remain mere hypotheses and it would not be profitable to discuss them here. We may add that though the analogy of the cardiac nervous mechanism, in which we can anatomically distinguish between augmentor and inhibitory fibres, justifies us in speaking of augmentor and inhibitory respiratory fibres as existing in the vagus nerve, we are not as yet able to distinguish them by anatomical methods. We may further add that so exquisitely sensitive is the respiratory centre to these afferent impulses, that stimuli too slight to produce any appreciable effect when applied to afferent nerves connected with an ordinary centre, such as a spinal reflex centre, may produce marked effects on the respiratory centre. For instance, the feeble electric current which is developed when the cut end of a divided vagus is replaced in the wound, the circuit between the cut end and the longitudinal surface of the nerve being closed through the blood or lymph of the wound, is often sufficient to develope inhibitory impulses. Again, when the connection of the respiratory centre with the lungs through the vagus nerves is abolished, not by section of the nerves but by freezing both nerves at some part of the course of each nerve (an operation which, while completely blocking the passage of impulses along the nerve-fibres, does not itself act as a stimulus) the effect on the respiratory movements is much more in the direction of increasing and prolonging the inspiratory act than of slowing the rhythm. Hence it would appear that what we have previously described as the result of dividing both vagus nerves, is partly due to the blocking of natural impulses and partly to the section of the nerves, and possibly to electric currents, developed as suggested above, acting as stimuli and thus giving rise to artificial impulses.

§ 368. The double or alternate respiratory action of the vagus nerves on which we have dwelt above may be taken as in a general way illustrative of the manner in which other afferent nerves and various parts of the cerebrum are enabled to influence respiration. As we have already said, and indeed know from daily experience, of all the apsychical nervous centres, the respiratory centre is the one which is most frequently and most deeply affected by nervous impulses from various quarters. Besides the changes brought about by the will (and when we breathe voluntarily we probably make use to some extent of the normal nervous machinery of respiration, working through this, rather than sending independent volitional impulses direct to the diaphragm and other respiratory muscles), we find that emotions and painful sensations alter profoundly the character of the respiratory movements. And though these effects may be partly indirect, (the emotion modifying the heart-beat or the tonus of the arteries, and so influencing the flow of blood through the respiratory centre,) they are chiefly due to the direct action of nervous impulses reaching that centre from higher parts of the brain. So also impulses from almost every sentient surface, or passing along almost every sensory nerve, may modify respiration in one direction or another. The influence in this way of stimuli applied to the skin is well known to all; but perhaps next to the vagus the nerve most closely connected with the respiratory centre is the fifth nerve, branches of which guard the nasal respiratory channels; the slightest stimulation of the nostrils at once affects the breathing and most frequently arrests it. The effects of stimuli of various strengths brought to bear on various nerves are very varied. Sometimes the result is an increase of inspiration; and that either by a quickening of the rhythm or by an increase of the individual breaths or by a combination of the two. Sometimes the result is an inhibition of inspiration accompanied or not by an increase of expiration, and sometimes, as when the stimulation causes a cough, the expiratory results may be out of all proportion to the modifications of inspiration. While in the case of some nerves, for instance, as we have seen, the superior laryngeal, and it is said the splanchnic nerves, the effects are exclusively or at least chiefly inhibitory of inspiration and augmentative of expiration, that is expiratory, and in others perhaps chiefly augmentative of inspiration or inspiratory, in the case of most nerves the effect may be according to circumstances either in the one direction or the other. Perhaps as a rule weak stimuli tend to augment and strong to inhibit inspiration; but the effects of artificially stimulating sensory nerves are complicated and often confused, because powerful afferent impulses by giving rise to pain may, through impulses generated by the pain itself and descending to the medulla from the brain, act in an indirect as well as in a direct manner; and the prominence of the indirect painful impulses will in any experiment depend on the anæsthetic used.

We may say, however, that in all cases the effect is very largely determined by the condition at the time being of the respiratory centre itself; and that is in turn determined not only by things which affect its nutrition, such as the character of the blood circulating in it, but also by the nature and amount of the other afferent impulses which are playing upon it at the same time. Thus, as we shall presently see, the effect of a stimulus applied to the vagus, when the respiratory centre is inadequately supplied with arterial blood, is not the same when the centre has its normal supply of normal blood. So also a stimulus, which applied to the vagus or to another nerve in an intact animal simply quickens inspiration, applied in an animal whose cerebral hemispheres have been removed will call forth a prolonged tetanic inspiratory gasp. The respiratory centre responds in fact in the most intricate and varied manner to nervous impulses proceeding from all parts of the body, and thus delicately adjusts the working of the respiratory pump to the needs of the economy.

§ **369**. The complicated nature of the respiratory centre is further shewn by the fact that it appears to consist of two lateral halves which normally work in unison and yet may be made to work independently. If the medulla oblongata be carefully divided in the middle line respiration may continue to go on in quite a normal fashion. If, however, one vagus be then divided, the respiratory movements, both costal and diaphragmatic, on the side of the body on which division of the vagus has taken place, become slower than those on the other side, so that the two sides are no longer synchronous; and a stimulus confined to one vagus affects the respiratory movements of that side of the body only. So also a section of a lateral half of the cord below the medulla stops the respiratory movements on that side alone.

§ **370**. Besides these nervous influences, however, there is another circumstance which perhaps above all others affects the respiratory centre, and that is the condition of the blood in respect to its respiratory changes; the more venous (less arterial) the blood, the greater is the activity of the respiratory centre. When by reason either of any hindrance to the entrance of air into the chest, or other interference with the due interchange between the blood and the pulmonary air or of a greater respiratory activity of the tissues, as during muscular exertion, the blood becomes less arterial, more venous, *i.e.* with a smaller charge of oxygen and more heavily laden with carbonic acid, the respiration from being normal becomes laboured. We may speak of normal breathing as *eupnœa*, and say that this, when the blood is insufficiently arterialized, passes into *dyspnœa*, an intermediate stage in which the respiratory movements are simply exaggerated being known as *hyperpnœa*. The modifications of breathing thus caused by deficient arterialization of blood are especially characterized by an increase in the total energy of the respiratory impulses generated, and in this respect differ from the modifications resulting from interference with the nervous arrangements such as those following upon section of the vagus nerves, in which case as we have seen the rhythm is much more profoundly affected than the amount. In dyspnœa the breathing is frequently quicker as well as deeper, there is an increase in the sum of efferent respiratory impulses, and the expiratory impulses, which in normal respiration are very slight, acquire a pronounced importance. As the blood becomes, in cases of obstruction, less and less arterial, more and more venous, the discharge from the respiratory centre becomes more and more vehement, and instead of confining itself to the usual tracts, and passing down to the ordinary respiratory muscles, overflows into other tracts and puts into action other muscles, until there is perhaps hardly a muscle in the body which is not made to feel its effects. The muscles which are thus more and more thrown into action are especially those tending to carry out or to assist expiration; and at last, if no relief is afforded, the violent but still definite respiratory movements give way to general convulsions of the whole body, which however have, to a certain extent, an expiratory character. With the onset of these convulsions dyspnœa is said to have passed into *asphyxia*. By the violence of these convulsions the whole nervous system becomes exhausted, the convulsions cease and death is ushered in through a few infrequent and long drawn breaths; but to this matter we shall return. The effect of venous blood then is to augment all those natural explosive decompositions of the substance of the central nervous system which give rise to respiratory impulses; it increases their amount, and also quickens their rhythm. The latter change, however, is much less marked than the former, the respiration being much more deepened than hurried, and the several respiratory acts are never so much hastened as to catch each other up, and so to produce an inspiratory tetanus like that resulting from stimulation of the vagus. On the contrary, especially as exhaustion begins to set in, the rhythm becomes slower out of proportion to the weakening of the individual movements.

§ **371**. The question naturally arises, Does this condition of the blood affect the substance of the central nervous system, that is to say, the respiratory centre in the medulla (and the subsidiary spinal nervous mechanisms) directly, or does it produce its effect by stimulating the peripheral ends of afferent nerves in various parts of the body, and, by the generation there of afferent impulses, indirectly modify the action of the central nervous system? Without denying the possibility that the latter mode of action may help in the matter, as regards not only the vagus, but all afferent nerves, the following facts seem to shew that the main effect is produced by the direct action of the blood on the central nervous system and indeed on the medullary respiratory centre itself. If the spinal cord be divided below the medulla oblongata, and both vagi be cut, want of proper aeration of the blood still produces an increased activity of the respiratory centre, as shewn by the increased vigour of the facial respiratory movements. If the supply of blood be cut off from the medulla by ligature of the carotid and intervertebral arteries dyspnœa is produced, though the operation produces at first no change in the blood generally, but simply affects the respiratory condition of the medulla itself by cutting off its blood-supply, the immediate result of which is an accumulation of carbonic acid and a paucity of available oxygen in the nervous substance of that region. If the blood in the carotid artery in an animal be warmed above the normal, a dyspnœa is produced which, though apparently not quite identical with the dyspnœa caused by imperfect arterialization of the blood, shews that the too high temperature of the blood directly affects the activity of the respiratory centre. We may conclude therefore that the condition of the blood affects respiration by acting directly on the respiratory centre. Moreover it is the medullary centre which, at all events in adult animals, is affected by the too venous blood, since after division of the spinal cord below the medulla, dyspnœic thoracic respiratory movements and convulsions do not follow upon exclusion of air. They are however stated to occur in new-born animals, indicating that the subsidiary mechanisms in the upper spinal cord of which we spoke in § 363 may be also affected by the too venous blood; but the doubts which we previously urged hold good in these cases also.

While the respiratory centre is thus being affected by the too venous blood, it is, until exhaustion begins to set in, more irritable, more easily and largely affected by afferent impulses than in its normal condition. During dyspnœa a stimulus which applied to the vagus or to some other sensory nerve under normal conditions would produce little or no effect, may start very powerful respiratory movements.

§ **372.** Deficient aeration produces two effects in blood: it diminishes the oxygen, and increases the carbonic acid. Do both of these changes affect the respiratory centre, or only one, and if so, which? When an animal is made to breathe an atmosphere containing nitrogen only, the exit of carbonic acid by diffusion is not affected, and the blood, as is proved by actual analysis, contains no excess of carbonic acid. Yet all the phenomena of dyspnœa are present, and if the experiment be continued, convulsions ensue and the animal dies in asphyxia. In this case the result can only be attributed to the deficiency of oxygen. On the other hand, if an animal be made to breathe an atmosphere rich in carbonic acid, but at the same time containing abundance of oxygen, though the breathing becomes markedly deeper and also somewhat more frequent, there is no culmination in a convulsive asphyxia, even when the quantity of carbonic acid in the blood, as shewn by direct analysis, is very largely increased. On the contrary, the increase in the respiratory movements may after a while pass off, the animal becoming unconscious, and appearing to be suffering rather from a narcotic poison than from simple dyspnœa; the excess of carbonic acid in the blood appears to affect other parts of the central nervous system, and especially portions of the brain, more profoundly than it does the respiratory centre. It has been maintained by some that while a deficiency of oxygen promotes inspiratory movements, an excess of carbonic acid stimulates the expiratory movements, the nervous mechanisms being so arranged that a lack of oxygen leads to an effort to get more of it and a too great load of carbonic acid to an effort to get rid of it; but the facts are opposed to the existence of any such teleological adaptation. It is obvious however that a lack of oxygen and an excess of carbonic acid affect the respiratory centre in very different ways, and that in ordinary cases of interference with the interchange in the lungs, as in deficient aeration, it is the lack of oxygen which plays the principal part in developing the abnormal respiratory movements. We may infer that it too is chiefly concerned in regulating the more normal respiration, but cannot as yet say what is the exact share to be attributed to the carbonic acid.

We may here point out that it is not to be supposed that each breath is determined by the condition of the blood flowing through the capillaries of the medulla at the moment preceding that breath, it is not to be imagined that each breath is the result of the lack of oxygen felt immediately before. On the contrary, as we have previously urged, the respiratory centre like the cardiac substance is an automatic centre, the respiratory impulses issue from it in rhythmic series as a result of the molecular changes, of the metabolism going on in its substance; and whatever affects that rhythm, whether few or many beats be influenced, produces its result by modifying that metabolism. A lack of oxygen in the blood, or a nervous impulse along an afferent fibre, both affect the centre by modifying its metabolism; but each probably affects it in a different way. It is beyond our present knowledge to explain how either the one or the other acts. We may imagine that a lack of oxygen on the other hand has a more profound effect in modifying the whole complex series of metabolic changes, the whole chain of building up and breaking down processes, thus in some way or other rendering the whole edifice so to speak more unstable; and that an afferent augmenting impulse (and possibly an excess of carbonic acid) acts rather after the fashion of what we are accustomed to call a stimulus, and fires off a larger amount of the already stored up explosive compounds. And we may further imagine that the special feature of the substance of the respiratory centre is that its metabolism is so arranged as to be thus, unlike that of other living substances, rendered unstable and more explosive, not simply diminished or deadened by a lack of oxygen. But these as yet are matters of speculation.

We may perhaps add that, under various nutritive conditions, the sensitiveness of the metabolism of the respiratory centre to lack of oxygen may vary widely. Thus while undoubtedly under the normal nutritive conditions afforded by the ordinary supply of normal blood to the medulla, lack of oxygen in that blood at once provokes increased respiratory movements, it need not do so under other nutritive conditions of the medulla. By transfusion a large proportion of the hæmoglobin holding blood may in an animal be gradually replaced by hæmoglobinless normal saline solution. In such a case the amount of oxygen brought to the medulla by the diluted blood must be greatly diminished, and yet, if the change be made sufficiently slowly, no conspicuous dyspnœa is produced; under the new strange nutritive conditions of the diluted blood the medulla is not affected in the same way as before by lack of oxygen.

§ **373**. There are reasons for thinking that conditions of the blood, other than variations in the amount of oxygen and carbonic acid, may also materially affect the working of the respiratory centre. It is a matter of common experience that muscular exertion, especially if at all excessive, increases the respiratory movements; violent exercise soon puts a man "out of breath." This increased activity of the respiratory centre is in large measure at all events caused by the character of the blood which during and for some little time after the movements is carried to the medulla, and not by any nervous impulses sent up to the medulla from the contracting muscles. This is shewn by the fact that if in an animal the spinal cord be divided in the dorsal or lumbar region and the hind limbs be powerfully tetanized, the respiratory movements are increased; the animal pants as it would do if it had been running. In such a case the only connection between the hind limbs and the respiratory centre is through the blood; it must be some change in the blood caused by the muscular contractions which affects the medulla when the blood passes from the hind limbs to be distributed by the heart to the medulla. Now when a muscle contracts its consumption of oxygen and production of carbonic acid, especially the latter (§ 63), are increased; the blood leaving the muscle is more venous than usual. Hence when many muscles are contracting powerfully the blood carried to the right side of the heart is more venous than usual; and we might expect that it is this unusually venous blood failing to be adequately arterialized in the lungs and hence reaching the medulla from the left side of the heart in a more venous, less completely arterialized condition than usual, which stirs up the respiratory centre to increased activity.

On examination however it is found that the blood leaving the left side of the heart in such cases, is not less arterialized but if anything more arterialized than usual. The increased respiratory movements induced by the changed blood soon prove sufficient or even more than sufficient to give the blood the extra quantity of oxygen and to remove the extra quantity of carbonic acid. Obviously the blood coming from the tetanized muscles affects the respiratory centre by virtue of some quality which, unlike that due to the deficiency of oxygen or excess of carbonic acid, is not immediately affected by the passage through the lungs. Whether the quality in question be dependent on an excess of sarcolactic acid, or on some other product or products of muscular metabolism, we do not as yet know. But the fact that substances in the blood may so affect the respiratory centre is interesting since it shews by how many safeguards the working of the respiratory centre is carefully adapted to the needs of the economy.

Thus a change in the circumstances surrounding an animal body, or a change in the body itself, may in one or more of several ways, by acting as a stimulus to some afferent nerves and so sending up afferent nervous impulses to the respiratory centre, or by interfering with the interchange of gases in the lungs, or by otherwise altering the proportion of the gases present in the blood reaching the respiratory centre, or by generating or increasing in that blood some substance or substances tending to affect the nutrition of the respiratory centre, affect the working of the all important breathing mechanism. And the affection so wrought has generally an adaptative character, it generally tends to protect the organism against the evil effects of the change.

§ **374**. *Apnœa.* When we attempt to hold our breath, we find that we can do this for a limited time only; sooner or later a breath must come; but, as is well known, the time during which we can remain without breathing may on occasion be much prolonged, if we first of all take a series of deep breaths. It is probable, though perhaps not distinctly proved, that when we breathe voluntarily, or when by an act of the will we hold the respiratory apparatus in any one respiratory phase, the nervous impulses, generated by the will, do not pass down by a direct and independent course to the respiratory muscles, but that the will makes use or modifies the activity of the medullary and spinal nervous respiratory mechanisms. The breath sooner or later inevitably follows because at last the natural impulses proceeding from the respiratory centre become too imperious to be any longer held in check by the impulses of volition passing down to the centre from the brain. The fact that a series of deep breaths, a thorough ventilation of the lungs postpones the victory of the unconscious centre, shews that such a ventilation in some way delays the development of the natural respiratory impulses. A similar but still more marked delay may often be seen in an animal under artificial respiration. If in a rabbit artificial respiration is carried on very vigorously for a while, and then suddenly stopped, the animal does not immediately begin to breathe. For a variable period no respiratory movements at all take place, and breathing when it does begin occurs gently and normally, only passing into dyspnœa if the animal is unable to breathe of itself; and even then the transition is quite gradual. Evidently during this period the respiratory centre is in a state of complete rest, no explosions are taking place, no respiratory impulses are being generated, and the quiet transition from this condition to that of normal respiration shews that the subsequent generation of impulses is attended by no great disturbance. Not only is the centre at rest, but it is less irritable than the normal; impulses along the vagus or other nerves which otherwise would produce respiratory explosions are now ineffectual. This state of things is known as that of *apnœa*, the converse of dyspnœa; and the longer pause in breathing mentioned above as possible after unusual ventilation of the lungs may be regarded as a brief apnœa.

Now it seemed natural to suppose that such a state of rest of the respiratory centre was brought about by the more than necessarily ample supply of oxygen afforded by the previous increased inspiratory movements; and indeed it was maintained that apnœa was the result of too great, just as dyspnœa is the result of too little arterialization of the blood reaching the respiratory centre. It was argued that owing to the increased vigour of the artificial respiratory movements the hæmoglobin of the arterial blood, which in normal breathing is not quite saturated with oxygen, became almost completely so, and that at the same time the quantity of oxygen simply dissolved in the blood became largely increased and its tension largely augmented. But there are reasons which render such a view untenable. In the first place there is no direct and satisfactory proof that in apnœa the arterial blood is overloaded with oxygen as supposed; indeed during the course of apnœa before it has come to an end the blood becomes distinctly less arterial, more venous than usual. In the second place apnœa if not entirely impossible, is much more difficult to bring about when both vagus nerves are divided, and if it does occur after section of the vagus nerves has not the same characters as ordinary apnœa. Now, when artificial respiration is being carried on section of the vagus nerves can have no effect on the quantity of oxygen taken up by the blood in the lungs. But the vagus nerves are the channel of impulses affecting the respiratory centre, and this relation of the apnœa to the vagus nerves suggests another and different interpretation of apnœa. As we have seen, expansion of the lung by acting in some way or other on the pulmonary terminations of the vagus nerve sends up along that nerve impulses which inhibit inspiration. And it is argued that repeated forcible inflations of the lungs produce apnœa by generating potent inhibitory impulses, which by a kind of summation of their effects in the medulla stop for a while the generation of respiratory impulses in the respiratory centre. This conclusion moreover is strongly supported by the fact that an apnœa may be produced, so long as the vagus nerves are intact, by forcible artificial respiration with hydrogen instead of atmospheric air; in other words, the inhibitory impulses generated in the vagus nerves by the inflation are sufficient wholly to neutralize the development of respiratory impulses which the deficient arterialization of the blood would otherwise have produced. The exact nature and development of such a summation of inhibitory impulses, especially in the presence of correlative augmentative impulses called forth by the corresponding successive collapses of the lungs, is too complex a matter to be dwelt on here. Moreover an apnœa may be produced though, as we have said, with difficulty after section of both vagus nerves; but in this case air and not hydrogen must be used for inflation, the use of the latter, in contrast to the result when the nerves are intact, leading to dyspnœa. The subject cannot as yet be considered as fully cleared up. That apnœa as ordinarily produced is in some way the result of inhibitory impulses generated by the inflations can however hardly be doubted.

§ **375**. *Secondary Respiratory Rhythm. Cheyne-Stokes Respiration.* A remarkable abnormal rhythm of respiration, first observed by Cheyne but afterwards more fully studied by Stokes, and hence called by their combined names, occurs in certain pathological cases. The respiratory movements gradually decrease both in extent and rapidity until they cease altogether, and a condition of apnœa, lasting it may be for several seconds, ensues. This is followed by a feeble respiration, succeeded in turn by a somewhat stronger one, and thus the respiration returns gradually to the normal, or may even rise to hyperpnœa or slight dyspnœa, after which it again declines in a similar manner. A secondary rhythm of respiration is thus developed, periods of normal or slightly dyspnœic respiration alternating by gradual transitions with periods of apnœa. The cause of the phenomena is not thoroughly understood. Whether the waning and waxing of the respiratory movements be due to corresponding rhythmic changes in the nutrition of the respiratory centre itself, or to a rhythmic increase and decrease of inhibitory impulses playing upon that centre from other parts of the body, for instance from higher regions of brain, has not yet been settled. It frequently appears in connection with a fatty condition of the heart, but has been met with in various maladies. Closely similar phenomena have been observed during sleep, under perfectly normal conditions; and this fact is rather in favour of the latter of the two explanations just given. The phenomena present a striking analogy with the 'groups' of heart-beats so frequently seen in the frog's ventricle placed under abnormal circumstances.

SEC. 8. THE EFFECTS OF CHANGES IN THE COMPOSITION AND PRESSURE OF THE AIR BREATHED.

§ **376.** The preceding sections have shewn us that the respiratory mechanism is arranged to work satisfactorily when the lungs are adequately supplied with air of the ordinary composition of, and at the ordinary pressure of the atmosphere. We have further seen that the mechanism can adapt itself within certain limits to changes in the composition and pressure of the air supplied. We may now consider briefly what takes place when those limits are overstepped. The most striking effects are seen, when, on account of occlusion of the trachea, or by breathing in a confined space, or for other reasons, a due supply of air not being obtained, normal respiration gives place, through an intermediate phase of dyspnœa, to the condition known as asphyxia; this, unless remedial measures be taken, rapidly proves fatal.

Asphyxia. As soon as the blood becomes less arterial, more venous than normal, the respiratory movements become deeper and at the same time more frequent; both the inspiratory and expiratory phases are exaggerated, the supplementary muscles spoken of § 334 are brought into play, and the rate of the rhythm is hurried. These effects, as we have seen, are chiefly to be ascribed to the deficiency of oxygen in the blood.

As the blood continues to become more and more venous the respiratory movements continue to increase both in force and frequency, a larger number of muscles being called into action and that to an increasing extent. Very soon, however, it may be observed that the expiratory movements are becoming more marked than the inspiratory. Every muscle which can in any way assist in expiration is in turn brought into play; and at last almost all the muscles of the body are involved in the struggle. The orderly expiratory movements culminate in expiratory convulsions, the order and sequence of which are obscured by their violence and extent. That these convulsions, through which dyspnœa merges into asphyxia, are due to a stimulation (by the venous blood) of the medulla oblongata, is proved by the fact that they fail to make their appearance when the spinal cord has been previously divided below the medulla, though they still occur after those portions of the brain which lie above the medulla have been removed. It is usual to speak of a 'convulsive centre' in the medulla, the stimulation of which gives rise to these convulsions; but if we accept the existence of such a centre we must at the same time admit that it is connected by the closest ties with the normal expiratory division of the respiratory centre, since every intervening step may be observed between a simple slight expiratory movement of normal respiration and the most violent convulsion of asphyxia. An additional proof that these convulsions are carried out by the agency of the medulla is afforded by the fact that convulsions of a wholly similar character are witnessed when the supply of blood to the medulla is suddenly cut off by ligaturing the blood vessels of the head. In this case the nervous centres, being no longer furnished with fresh blood, become rapidly asphyxiated through lack of oxygen, and expiratory convulsions quite similar to those of ordinary asphyxia, and preceded like them by a passing phase of dyspnœa, make their appearance. Similar 'anæmic' convulsions are seen after a sudden and large loss of blood from the body at large, the medulla being similarly stimulated by the lack of arterial blood. In ordinary fainting, which is loss of consciousness due to an insufficient supply of blood to the brain, the diminution of blood supply is not great enough to produce these convulsions.

Such violent efforts speedily exhaust the nervous system; and the convulsions after being maintained for a brief period suddenly cease and are followed by a period of calm. The calm is one of exhaustion; the pupils, dilated to the utmost, are unaffected by light; touching the cornea calls forth no movement of the eyelids, and indeed no reflex actions can anywhere be produced by the stimulation of sentient surfaces. All expiratory active movements have ceased; the muscles of the body are flaccid and quiet; and though from time to time the respiratory centre gathers sufficient energy to develope respiratory movements, these resemble those of quiet normal breathing, in being, as far as muscular actions are concerned, almost entirely inspiratory. They occur at long intervals, like those after section of the vagi; and like them are deep and slow. The exhausted respiratory centre takes some time to develope an inspiratory explosion; but the impulse when it is generated is proportionately strong. It seems as if the resistance which had in each case to be overcome was considerable, and the effort in consequence, when successful, productive of a large effect.

Very soon, these inspiratory efforts become less frequent; their rhythm becomes irregular; long pauses, each one of which seems a final one, are succeeded by several somewhat rapidly repeated inspirations. The pauses become longer, and the inspiratory movements shallower. Each inspiration is accompanied by the contraction of accessory muscles, especially of the face, so that each breath becomes more and more a prolonged gasp. The inspiratory gasps spread into a convulsive stretching of the whole body; and with extended limbs, and a straightened trunk, with the head thrown back, the mouth widely open, the face drawn, and the nostrils dilated, the last breath is taken in.

Thus we are able to distinguish three stages in the phenomena which result from a continued deficiency of air: (1) A stage of dyspnœa, characterized by an increase of the respiratory movements both of inspiration and expiration. (2) A convulsive stage, characterized by the dominance of the expiratory efforts, and culminating in general convulsions. (3) A stage of exhaustion, in which lingering and long-drawn inspirations gradually die out. When brought about by sudden occlusion of the trachea these events run through their course in about 4 or 5 minutes in the dog, and in about 3 or 4 minutes in the rabbit. The first stage passes gradually into the second, convulsions appearing at the end of the first minute. The transition from the second stage to the third is somewhat abrupt, the convulsions suddenly ceasing early in the second minute. The remaining time is occupied in the third stage.

The duration of asphyxia varies not only in different animals but in the same animal under different circumstances. Newly born and young animals need much longer immersion in water before death by asphyxia occurs than do adults. Thus while in a full-grown dog recovery from drowning is unusual after 1½ minutes, a new-born puppy has been known to bear an immersion of as much as 50 minutes. The cause of the difference lies in the fact that in the quite young or rather just born animal the respiratory changes of the tissues are much less active. These consume less oxygen, and the general store of oxygen in the blood has a less rapid demand made upon it. The respiratory activity of the tissues may also be lessened by a deficiency in the circulation; hence bodies in a state of syncope at the time when the deprivation of oxygen begins can endure the loss for a much longer period than can bodies in which the circulation is in full swing. There being the same store of oxygen in the blood in each case, the quicker circulation must of necessity bring about the speedier exhaustion of the store. So also anæsthetics may diminish the effects and delay the final results; large doses of anæsthetics may prevent the exaggerated and convulsive movements. In many cases of drowning, death is hastened by the entrance of water into the lungs.

By training, the respiratory centre may be accustomed to bear a scanty supply of oxygen for a much longer time than usual before dyspnœa sets in, as is seen in the case of divers.

The phenomena of slow asphyxia, where the supply of air is gradually diminished, are fundamentally the same as those resulting from a sudden and total deprivation. The same stages are seen, but their development takes place more slowly.

§ **377**. Deficiency of air results not only in a diminution of the oxygen but also in an increase of the carbonic acid of the blood. We have seen however (§ 372) that the phenomena of asphyxia are in the main due to the former, and that the accumulation of carbonic acid in the blood has subsidiary effects only.

If the percentage of oxygen in the inspired air be increased instead of diminished, the total pressure of the atmosphere remaining the same, the partial pressure of the oxygen alone being changed, no marked results follow. We have already seen (§ 354) that the percentage of oxygen in the ordinary atmosphere leaves a wide margin of safety, and that (§ 374) the phenomena of apnœa are in the main at least to be explained as the result not of an increase in the oxygen of the blood but of nervous impulses ascending the vagus nerves. We have no satisfactory evidence that, provided the respiratory mechanism is in good working order, an increase of oxygen in the inspired air even to a whole atmosphere seriously modifies the respiratory act; and it may be doubted whether any effect is produced even when the mechanism is impaired.

§ **378**. The composition of the atmosphere, the pressure remaining the same, may be modified by the introduction of foreign gases. To some of these the respiratory mechanism is indifferent; for instance, hydrogen may be substituted for nitrogen without any change in the respiration, provided of course that the oxygen is not diminished. Other gases may produce poisonous effects, either by interfering with some of the respiratory processes or in other ways. Thus carbon monoxide, by combining with the hæmoglobin of the red corpuscles, and so preventing the corpuscles from acting as oxygen carriers, produces asphyxia through deficiency of oxygen. Sulphuretted hydrogen interferes with the oxygenation of the blood by acting as a reducing agent. Some gases while allowing the ordinary respiratory changes of the blood to go on as usual produce toxic effect by acting on one or other of the tissues. Thus, as we have seen, an excess of carbonic acid in the blood seems to have a special effect on the central nervous system and so acts as a narcotic poison. The peculiar effects of nitrous oxide (laughing gas) are similarly due to the direct action of the gas in the blood on the central nervous system. Some gases are irrespirable and may interfere with respiration, even causing suffocation, on account of their causing spasm of the glottis, and this is said to be, to a certain extent, the case with an atmosphere which is wholly or largely composed of carbonic acid.

§ 379. *The Effects of Changes in Atmospheric Pressure. Diminution of pressure.* The partial pressure of the oxygen in the inspired air may be changed, not only by altering the composition of the air entering at the ordinary atmospheric pressure, but also by altering the total pressure of the atmosphere without changing its composition. The results of the latter are however complicated; we have then to deal not merely with the effects on the interchange of gases in the lungs but with the effects on the whole organism. All the complicated machinery of the body is adapted and arranged to work under what we may call ordinary atmospheric pressure, that is to say, within the limits of 760 mm. mercury at the sea level and about 500 mm., corresponding to an altitude of 6000 feet, this being the range of ordinary human dwellings. Any great increase or decrease of pressure beyond these limits will affect not only the exit of carbonic acid from and the entrance of oxygen into the blood, but, in varying degree, all the physical and chemical processes of the body. A gross instance of this is seen when an animal is suddenly subjected to a great diminution of pressure, as when it is placed in the receiver of an air-pump and the receiver rapidly exhausted. The animal is soon thrown into fatal convulsions, which are in part, but only in part, due to the liberation of gas from the blood within the blood vessels; the gas so set free mechanically interferes with the circulation, as by obstructing the play of the cardiac valves, or by plugging the smaller blood vessels, and thus helps to bring the machine to a standstill. The free gas found in the vessels upon examination after death is said to be composed chiefly of nitrogen, the carbonic acid and the oxygen, which probably were also set free, having been reabsorbed before the examination was made.

But, quite apart from gross effects of this kind, it is very obvious that the organism must in many ways suffer from a diminution of pressure. The complex and delicately balanced vascular system is constructed to work at the ordinary atmospheric pressure. The force of the heart-beat and the tonic contraction of the small arteries are, so to speak, pitched to meet the influence exerted on the outside of the blood vessels by the ordinary pressure of the atmosphere; and any great diminution of that pressure must produce a greater or less disarrangement of the vascular mechanism until it is counterbalanced by some compensating changes. And a little reflection will supply many other instances.

We have already called attention (§ 354) to the fact that, the total pressure of the atmosphere remaining the same, the partial pressure of the oxygen in the inspired air may be reduced as low as about 76 mm. (10 p.c.) without seriously modifying the respiration. In order to attain this diminution of the partial pressure of the oxygen without changing the composition of the atmosphere, the total pressure of the atmosphere must be reduced to the limit of 300 mm., corresponding to an altitude of 17000 feet. Now it is a matter of common experience that in ascending a mountain "distress" is felt long before such an altitude is reached. The distress felt on such occasions is probably due not so much, if indeed at all directly, to the diminution of oxygen as to a general disarrangement of the organism and perhaps more particularly of the vascular system. The nose-bleeding which is so frequent an occurrence under the circumstances shews that the minute blood vessels more directly exposed to the diminution of pressure are profoundly affected by it; and what is true of them is, probably, in various ways and to different degrees true of the whole vascular system. The breathlessness which is so marked a feature on these occasions seems due not so much to the fact that the blood which reaches the respiratory nervous centres is deficient in oxygen, as to the fact that the troubled vascular system fails to deliver to those centres their blood in an adequate fashion.

It is a feature of the vascular system, and indeed of the other mechanisms of the body, in which nervous factors intervene, that they possess the power of adapting themselves to changed conditions; and as it is well known, the human organism somewhat rapidly becomes accustomed to these moderate altitudes. Practice and custom have far less effect, though they have some, on the more fundamental processes depending on the actual supply of oxygen; and it is at the extreme altitudes, where in addition to the other troubles a deficiency of oxygen definitely makes itself felt, that the body seems to fail in adapting itself to the new circumstances.

The addition of these troubles not directly respiratory in nature, when the supply of oxygen is diminished by a diminution of the total pressure, perhaps explains why though an adequate lowering of pressure will produce asphyxia, that asphyxia is somewhat different from the ordinary asphyxia due to deprivation of air or oxygen. Convulsions which are essential to ordinary asphyxia are at times wholly absent; the nervous system under the peculiar conditions does not respond to the stimulus of the lack of oxygen; and other nervous symptoms, such as a rapid onset of feebleness amounting almost to paralysis, are apt to make their appearance.

§ 380. *The Effects of Increase of Atmospheric Pressure.* These are in many ways remarkable. Up to a pressure of several atmospheres of air, the only symptoms which present themselves are those somewhat resembling narcotic poisoning. The animal becomes sleepy and stupid, the result probably not so much of respiratory changes, as of the effects of the increased pressure on the whole organism to which we have just alluded. At a pressure however of 15 atmospheres of air, or what amounts to the same thing, of 3 atmospheres of oxygen, and upwards, a very remarkable phenomenon presents itself. The animals die of asphyxia and convulsions, exactly in the same way as when oxygen is deficient. Corresponding with this it is found that the production of carbonic acid is diminished. That is to say, when the pressure of the oxygen is increased beyond a certain limit, the oxidations of the body are diminished, and with a still further increase of the oxygen are arrested altogether. The oxidation of phosphorus is perhaps analogous; at a high pressure of oxygen phosphorus will not burn. Not only animals but plants, bacteria, and organised ferments, are similarly killed by a too great pressure of oxygen.

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SEC. 9. THE RELATIONS OF THE RESPIRATORY SYSTEM TO THE VASCULAR AND OTHER SYSTEMS.

§ **381**. Many events in the body shew the influence which the respiratory movements exert on the circulation. When the brain of a living mammal is exposed by the removal of the skull, a rhythmic rise and fall of the cerebral mass, a pulsation of the brain, quite distinct from the movements caused by the pulse in the arteries of the brain, is observed; and upon examination it will be found that these movements are synchronous with the respiratory movements, the brain rising up during expiration and sinking during inspiration. They disappear when the arteries going to the brain are ligatured, or when the venous sinuses of the dura mater are laid open so as to admit of a free escape of the venous blood. They evidently arise from the expiratory movements in some way hindering and the inspiratory movements assisting the return of blood from the brain. We have already (§ 116) stated that during inspiration the pressure of blood in the great veins may become negative, *i.e.* may sink below the pressure of the atmosphere; and a puncture of one of these veins may cause death by air being actually drawn into the vein and thus into the heart during an inspiratory movement. When the veins of an animal are laid bare in the neck and watched, the so-called *pulsus venosus* may be observed in them, that is, they swell up during expiration and diminish again during inspiration. And indeed a little consideration will shew that the expansion and contraction of the chest must have a decided effect on the flow of blood through the thoracic portion of, and thus indirectly on that through the whole of, the vascular system.

This is well illustrated by the effects of respiration on arterial blood-pressure. We have seen, while treating of the circulation, that the arterial blood-pressure curves are marked by undulations, which, since their rhythm is synchronous with that of the respiratory movements, are evidently in some way connected with respiration. Similar undulations may be observed in the pulse tracings taken from man.

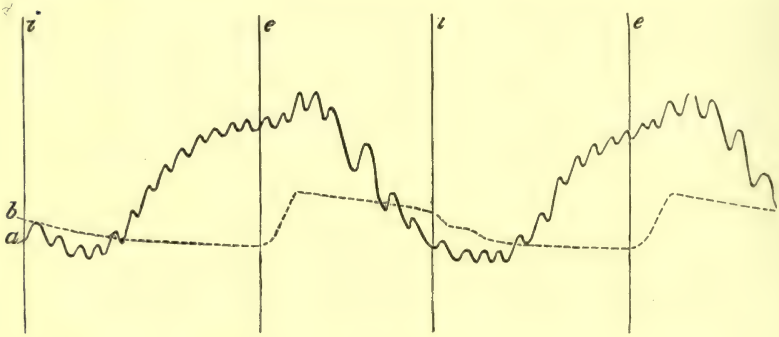

Fig. 85. Comparison of Blood-Pressure Curve with Curve of Intra-thoracic Pressure. (Dog.)

a is the blood-pressure curve taken by means of a mercury manometer; it shews the respiratory undulations, the slower beats on the descent being very marked. *b* is the curve of intra-thoracic pressure obtained by connecting one limb of a manometer with the pleural-cavity. Inspiration begins at *i*, expiration at *e*. With the beginning of inspiration (*i*) the expansion of the chest causes a marked fall of the mercury in the intra-thoracic manometer; but the effect soon diminishes, since the lessening of intra-thoracic pressure does not bear on the manometer alone but on the lungs also; and as the lungs expand more and more the fall in the mercury becomes less and less until towards the end of inspiration the curve becomes very nearly a straight line. Conversely, the return of the chest at the beginning of expiration (*e*) produces at first a marked rise of the mercury in the manometer; but this soon ceases as the air leaves the chest and the lungs shrink, whereupon the mercury falls slowly.

When these undulations of the blood-pressure curve are compared carefully with the respiratory movements or with the variations of intra-thoracic pressure, what is most commonly observed is that while the blood-pressure, on the whole, rises during inspiration and falls during expiration neither the rise nor the fall is exactly synchronous with either inspiration or expiration. Fig. 85 shews two tracings from a dog taken at the same time, one, *a*, being the ordinary blood-pressure curve from the carotid, and the other, *b*, representing the condition of the intra-thoracic pressure as obtained by carefully bringing a manometer into connection with the pleural cavity. On comparing the two curves it is evident that neither the rise nor the fall of arterial pressure coincides exactly either with inspiration or with expiration. At the beginning of inspiration (*i*) the arterial pressure is seen to be falling; it soon however begins to rise, but does not reach the maximum until some time after expiration (*e*) has begun; the fall continues during the remainder of expiration, and passes on into the succeeding inspiration. This suggests the idea that, while inspiration tends to increase and expiration to diminish the blood-pressure, there are causes at work which in each case delay the effect.

Extended observations however shew that such a relation as that shewn in the figure though frequent is not constant. In fact the effects of the respiratory movements on blood-pressure are found to vary very widely according as the respiration is quick or slow, easy and shallow, or laboured and deep, and especially as the air enters into the chest readily or with difficulty. Moreover, respiratory undulations of blood-pressure are seen not only with natural but also with artificial respiration; in the latter the mechanical conditions are to a large extent the reverse of those of the former, and might fairly be expected to affect the circulation in a different way. The causation of these respiratory undulations is in fact complex. The respiratory act affects the vascular system in several different ways, and the general effect varies according as one or other influence is predominant. These several actions are sufficiently interesting and important to deserve discussion.

§ **382**. The heart and great blood vessels are, like the lungs, placed in the air-tight thoracic cavity, and are subject like the lungs to the pumping action of the respiratory movements. Were there no lungs present in the chest, the whole force of the expansion of the thorax in inspiration would be directed to drawing blood from the extra-thoracic vessels towards the heart, and conversely in expiration the effect of the return of the thorax to its previous dimensions would be to drive the blood thus drawn in back again from the heart towards the extra-thoracic vessels. And, even in the presence of the lungs, some of this effect is still felt. The main purpose and the main result of the expansion of the chest in inspiration is of course to draw air into the lungs; by that expansion the air in the pulmonary alveoli is rarified and brought to a lower pressure than that of the atmosphere outside the chest; and the difference of pressure thus set up leads to an inrush of inspired air until an equilibrium of pressure is established between the air in the lungs and that outside the chest. Before however the inspired air can fill a pulmonary alveolus the elastic walls of the alveolus have to be distended, and that distension is effected by means of the pressure which causes the inspired air to enter. Part of the atmospheric pressure in fact which causes the entrance of the air into the lung is spent in overcoming the elasticity of the pulmonary passages and cells. So that while by the inrush of inspired air the difference of pressure between the air inside the pulmonary alveoli and that outside the chest, brought about by the thoracic expansion, is completely neutralized, the difference between the pressure to which the parts lying within the thorax but outside the lungs are exposed and that outside the chest is not so completely neutralized. The pressure on these parts always falls short of the pressure of the atmosphere by the amount of pressure necessary to counterbalance the elasticity of the pulmonary passages and alveoli. Consequently, any structure lying within the thorax but outside the lungs, is never, even at the conclusion of an inspiration when the lungs are filled with air, subject to a pressure as great as that of the atmosphere. And, since the fraction of the atmospheric pressure which is thus spent in distending the lungs increases as the lungs become more and more stretched, it follows that the fuller the inspiration the greater is the difference between the pressure on structures within the thorax but outside the lungs and the ordinary pressure of the atmosphere. Now we have seen that the pressure necessary to counterbalance the elasticity of the lungs, when they are completely at rest (in the pause between expiration and inspiration), is in man about 5 to 7 mm. of mercury, and that when the lungs are fully distended, as at the end of a forcible inspiration, the pressure rises to as much as 30 mm. of mercury. Hence at the height of a forcible inspiration the pressure exerted on the heart and great vessels within the thorax is 30 mm. less than the ordinary atmospheric pressure of 760 mm., and even when the chest is completely at rest, at the end of an expiration, the pressure on the heart and great vessels is slightly (by about 5 mm. mercury) below that of the atmosphere. We may add that any obstacle to the free ingress of the inspired air, any difficulty in the full expansion of the pulmonary alveoli, of course increases the negative pressure to which the thoracic structures outside the lungs are subjected by the expansion of the chest. Hence when the trachea is closed a very large part of the thoracic expansion is directed to increasing the negative pressure around the heart and great blood vessels.

During an inspiration then the pressure around the heart and great blood vessels becomes considerably less than that of the atmosphere on the vessels outside the thorax. During expiration this pressure returns towards that of the atmosphere, but in ordinary breathing never quite reaches it. It is only in forcible expiration that the pressure on the thoracic vascular organs reaches or exceeds that of the atmosphere. But if during inspiration the pressure bearing on the right auricle and the venæ cavæ becomes less than the pressure which is bearing on the jugular, subclavian, and other veins outside the thorax, this must result in an increased flow from the latter into the former. Hence during each inspiration a larger quantity of blood enters the right side of the heart. This probably leads to a stronger stroke of the heart, and at all events causes a larger quantity to be ejected by the right ventricle; this causes a larger quantity to escape from the left ventricle, and thus more blood is thrown into the aorta, and the arterial pressure proportionately increased. During expiration the converse takes place. The pressure on the intra-thoracic blood vessels returns to the normal, the flow of blood from the veins outside the thorax into the venæ cavæ and right auricle is no longer assisted, and in consequence less blood passes through the heart into the aorta, and arterial pressure falls again. During forced expiration, the intra-thoracic pressure may be so great as to afford a distinct obstacle to the flow from the veins into the heart.

The effect of the respiratory movements on the arteries is naturally different from that on the veins. During inspiration the diminution of pressure in the thorax around the aortic arch tends to expand the aortic arch, and thus to check the onward flow of blood, and to diminish the pressure of blood within the aorta. During expiration, the increase of pressure outside the aortic arch of course tends to increase also the blood-pressure within the aorta, acting in fact just in the same way as if the coats of the aorta themselves contracted. Thus as far as arterial blood-pressure is concerned the effects of the respiratory movements on the great veins and great arteries respectively are antagonistic to each other; the effect on the veins being to increase arterial pressure during inspiration and to diminish it during expiration, while the effect on the arteries is to diminish arterial pressure during inspiration and to increase it during expiration. But we should naturally expect the effect on the thin-walled veins to be greater than that on the stout thick-walled arteries, so much so that the direct effect on the arteries may be neglected. That is to say, we should expect the blood-pressure to rise during inspiration and to fall during expiration. This as we have seen is frequently the case, and indeed when the breathing is deep and laboured, and especially during violent and sudden respiratory movements, the influence in this direction on the blood-pressure curve of the pumping action of the chest is unmistakeable.

In attempting however to estimate the effect of the respiratory movements on blood-pressure we must bear in mind what is taking place in the abdomen. In inspiration the descent of the diaphragm compresses the abdominal viscera, and so, while at the very first it drives a quantity of blood onward along the inferior vena cava, subsequently hinders the upward flow from the abdomen and lower limbs; at the same time by compressing the abdominal aorta, it tends to raise the pressure in the thoracic aorta and its branches, while lowering that of the abdominal aorta and its branches. The effect of easy expiration would be the converse of this; but in forced expiration the pressure of the contracting abdominal muscles would, as in inspiration, first tend to drive the blood onward along the vena cava but subsequently to hinder the flow both along the vena cava and the aorta. The effect of the abdominal movements therefore is mixed and variable, and their influence on the blood-pressure in the femoral artery must be different from that on the radial artery or other branch of the thoracic aorta. It is difficult to predict what in all cases the effect would be; and the matter cannot be settled by eliminating the movements of the diaphragm through section of the phrenic nerves, since in such a case the whole working of the respiratory pump is materially affected.

§ **383**. In addition to the influence thus exerted by the thoracic movements on the great veins leading to, and the great arteries leading from the heart, we have to consider the behaviour of the pulmonary vessels themselves under the varying thoracic pressure. These, like the venæ cavæ and aorta, tend to expand under the influence of the inspiratory expansion of the chest, and thus to become fuller of blood, very much as they would if the whole lung were placed under a large cupping-glass. The first effect of this increased filling of the pulmonary vessels would be to retain for a while a certain quantity of blood in the lungs and thus to lessen the amount falling into the left auricle. But this would be temporary only; and the widening of the pulmonary vessels would speedily produce an exactly contrary effect, namely, an increased flow through the lungs due to the diminished resistance offered by the widened passages. Conversely, the first effect of expiration would be an increased flow into the left auricle due to the additional quantity of blood driven onwards by the partial collapse of the pulmonary vessels, followed by a more significant diminished flow caused by the greater resistance now offered by the narrower vascular channels. Thus the effect of inspiration in this way would be first to diminish the flow into the left auricle and so into the left ventricle, but afterwards, for the rest of the inspiration until the beginning of expiration, to increase the flow into the ventricle; while conversely the effect of expiration would be first, for a brief period, to increase and afterwards, during the rest of the movement, to diminish the flow of blood into the left ventricle. Further, while this may be considered as the effect on the pulmonary vessels, large and small taken altogether, the influence both of the thoracic negative pressure during inspiration, and the return in a positive direction during expiration, will bear more on the thin-walled pulmonary veins than on the stouter pulmonary artery; that is to say, as inspiration becomes established, there will be a diminution of pressure in the pulmonary veins greater than that in the pulmonary artery, and this will be an additional influence favouring the flow into the left ventricle; during expiration a similar difference of effect will be felt in the contrary direction. During the increase of flow into the ventricle, the quantity of blood ejected at each stroke will increase, and each stroke will (§ 162) be increased in vigour, in consequence of which the arterial pressure will rise. Conversely, during the decrease of flow into the ventricle, the arterial pressure will fall. Hence the general effect of the movements of the chest on the pulmonary vessels will be during the beginning of inspiration to continue the lowering of arterial pressure which was taking place during expiration but subsequently to raise the arterial pressure; and conversely at the beginning of expiration to continue the rise of arterial pressure which was taking place during inspiration but subsequently to lower arterial pressure. In ordinary breathing, as we have seen, what may be considered as the normal relations of blood-pressure to the respiratory movements are precisely of this kind.

§ **384**. Effects of the respiratory movements, however, are seen not only in natural but also in artificial respiration. When, for instance, in an animal under urari, artificial is substituted for natural respiration, undulations of the blood-pressure curve, synchronous with the respiratory movements, are still observed (Fig. 86), though generally less in extent than those seen under natural conditions.

Now in artificial respiration, the mechanical conditions under which the thoracic viscera are placed as regards pressure are the exact opposite of those existing during natural respiration, for when air is blown into the trachea to distend the lungs, the pressure within the chest is increased instead of diminished. Under these circumstances, applying the considerations laid down in the preceding paragraph with regard to natural respiration, we should expect to find that while the first effect of an artificial inspiration would be to drive an additional quantity of blood out of the lungs into the left ventricle, and thus to raise arterial pressure, this would be in turn followed by a fall of arterial pressure due to the increased resistance offered both to the passage of blood through the lungs and to the entrance of blood through the venæ cavæ into the right auricle. Conversely, the effect of the succeeding expiration would be an initial continuance of the fall of arterial pressure succeeded by a rise. In other words, we should expect to find in artificial respiration effects exactly the reverse of those which we find in normal respiration; and indeed in many curves of blood-pressure taken during artificial respiration this is the case.

Both in natural and in artificial respiration, however, the features of the blood-pressure curve vary according as the breathing is hurried or slow, shallow or deep, and according to the facility with which air enters the chest, so much so that at times the blood-pressure curves of natural and artificial respiration may closely resemble each other. And a little consideration would lead us to expect this.

We have seen that the rise in arterial pressure which marks the respiratory undulation is in the main due to a temporary greater amount of blood thrown into the aorta by the left ventricle, and that correspondingly the fall of pressure completing the undulation is in the main due to a temporary lessening of the amount so thrown. Though the causes discussed in § 382 undoubtedly make themselves prominent in laboured and violent respiratory movements, we may conclude that in ordinary respiration, both natural and artificial, the main events producing the respiratory undulations are those discussed in § 383. We may restate the conclusions of that discussion by saying that the respiratory movements affect the amount of flow of blood into the left ventricle, and so the discharge of blood from the left ventricle into the aorta, in two main ways. In the first place, through the widening or narrowing of the pulmonary vessels they alter the capacity of the vessels to hold blood for the time being. In the second place, in consequence of the difference of resistance, occasioned by the widening or narrowing, they alter the rate of flow through the pulmonary vessels. The first factor is a brief and passing one; the extra room due to widening is soon filled up, the narrowed vessels soon discharge the quantity which they can no longer hold. But the second factor is a more lasting one; so long as in the respiratory movement the vessels remain widened or narrowed so long is the rate of flow increased or diminished. These two factors produce opposite effects, and hence the total result of any particular kind of respiration will depend on their relative prominence. With quickly repeated respiratory movements the first factor comes to the front; when the respiratory movements are more slowly repeated and more slowly carried out the second factor is the more potent. Hence it comes about that in quickly repeated artificial respiration where the first factor is predominant, and the prominent effect of each inflation is to diminish the capacity of, and so to empty the pulmonary vessels and to increase the flow into the ventricle whereby the pressure rises in inflation, that is in inspiration, the blood-pressure curve simulates that of a slowly repeated natural respiration, where the pressure also rises in inspiration, but where, the second factor being predominant, the rise of pressure brought about by each inspiration is due mainly to the more rapid flow through the widened pulmonary vessels. And other illustrations of a like kind could be given.

§ **385**. Besides the mechanical effects of the respiratory movements the vascular system is influenced by respiration through the changes in the gases of the blood.

Changes in the blood may affect on the one hand the vaso-motor system and on the other hand the heart. They may further affect the heart either directly by acting on the cardiac tissues or indirectly by means of the inhibitory and augmentor cardiac nerves. They may also probably affect the peripheral vessels, not only through vaso-motor nerves but by acting directly on the walls of the smaller vessels. We have indications of an action of respiration on the cardio-inhibitory system, even in normal quiet respiration. One striking feature of the respiratory undulation in the blood-pressure curve of the dog[1] is the fact that the pulse-rate is quickened during the rise of the undulation and becomes slower during the fall; see Fig. 85. A similar influence may be seen in pulse-tracings taken from man. The quickening of the beat might be considered as itself partly accounting for the rise of pressure, or on the other hand it might be urged that the increased flow of blood which causes the rise of pressure, at the same time leads to the quickening of the beat, were it not for one fact, viz. that the difference is at once done away with, without any other essential change in the undulations, by section of both vagus nerves. Evidently the slower pulse during the fall is caused by a coincident stimulation of the cardio-inhibitory centre in the medulla oblongata, the quicker pulse during the rise being due to the fact that, during that interval, the centre is comparatively at rest. We have here indications that, while the respiratory centre in the medulla oblongata is at work, sending out rhythmic impulses of inspiration and expiration, the neighbouring cardio-inhibitory centre is, as it were by sympathy, thrown into an activity of such a kind that its influence over the heart waxes with each expiration and wanes with each inspiration. We cannot as yet explain exactly the manner in which the activity of the one centre influences that of the other; it may be that during the expiratory phase the blood reaching the medulla is not quite so well arterialized, especially as far as the escape of carbonic acid is concerned, as during the inspiratory phase, and that the cardio-inhibitory centre is sufficiently sensitive to appreciate the slight difference; but of this we cannot be sure.

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[1] In the rabbit, the respiratory undulations, though well marked, present a very small difference of pulse-rate in the rise and fall.

§ **386**. When through interference with the pulmonary interchange the blood sent out from the left ventricle becomes and continues to be less arterialized than usual, the effects on both the heart and the vaso-motor system become conspicuous. The rhythm of the heart-beats is most distinctly slowed. This, under ordinary circumstances when the vagus nerves are intact, is probably in part the result of vagus inhibition, the venous blood, as suggested above, stimulating the cardio-inhibitory centre in the medulla. But the slowing is not wholly caused in this way, for it is still conspicuous in an animal placed under urari and with both vagus nerves divided. Compare curves 3 and 4 with 1 and 2 in Fig. 86. How this slowing is brought about is not very clear. When venous blood is sent through an excised heart, the beat is, it is true, slowed, but it is also and still more conspicuously weakened. Now when the blood becomes too venous, as is shewn in Fig. 86, even after the action of the vagus nerves has been eliminated by section and also by urari, the slowing is out of proportion to the weakening, since, as we shall presently see, the blood-pressure rises; and though that rise is chiefly due to vaso-motor constriction, still it could not take place if the cardiac stroke were very notably weakened. It may be that the venous blood stimulates the cardiac augmentor mechanism in such a way as to bring about an augmentation of the cardiac stroke rather than a quickening of the rhythm; but this has not been definitely proved. In any case a slow beat, with such a maintenance of the strength of the cardiac strokes as permits the continuance for some considerable time of a high blood-pressure, is met when the arterialization of the blood is interfered with. Sooner or later, however, the deficiency of oxygen in the blood diminishes the store of explosive compounds in the cardiac muscular substance, the beats lessen in force, often shewing a temporary increase in frequency, and soon become irregular.

§ **387**. The effects of deficient arterialization on the vaso-motor system are well shewn when in an animal placed under a moderate dose of urari so as to eliminate the complications due to contractions of the skeletal muscles, with both vagi divided so as to ensure the elimination of inhibitory impulses from the medulla, artificial respiration is suspended. Soon after the respiration is stopped, a very large but steady rise of pressure is observed. See Fig. 86. The rise so witnessed is very similar to that brought about by powerfully stimulating a number of vaso-constrictor nerves; and there can be no doubt that it is due to the venous blood stimulating the vaso-motor centre in the medulla, and thus causing constriction of the small arteries of the body, especially those of the splanchnic area, since as we shall see, in speaking of the skin, a too venous blood leads to a widening of the cutaneous arteries. We say 'stimulating the medullary vaso-motor centre,' because, though we must admit that, since a rise of pressure follows upon dyspnœa when the spinal cord has been previously divided below the medulla, the venous blood may stimulate other vaso-motor centres in the spinal cord and possibly even act directly on local peripheral mechanisms, yet the fact that the rise of pressure is much less under these circumstances shews that the medullary centre plays the chief part. As we have just said, the effect of this vaso-constriction in raising the pressure, if not assisted by an increase, at all events, is not neutralized by an adequate decrease of the cardiac stroke. Upon the cessation of the artificial respiration, the respiratory undulations of course cease also, so that the blood-pressure curve rises at first steadily in almost a straight line broken only by the heart-beats; yet after a while new undulations, the so-called Traube or Traube-Hering curves, make their appearance (Fig. 85. 2, 3), very similar to the previous ones, except that their curves are larger and of a more sweeping character. These new undulations, since they appear in the absence of all thoracic or pulmonary movements, passive or active, and are witnessed even when both vagi are cut, must be of vaso-motorial origin; the rhythmic rise must be due to a rhythmic constriction of the small arteries, and this probably is caused by a rhythmic discharge from vaso-motor centres, and especially from the medullary vaso-motor centre. The undulations are maintained as long as the blood-pressure continues to rise. With the increasing venosity of the blood, however, both the vaso-motor centres and the heart become enfeebled; the undulations disappear, and the blood-pressure rapidly sinks.

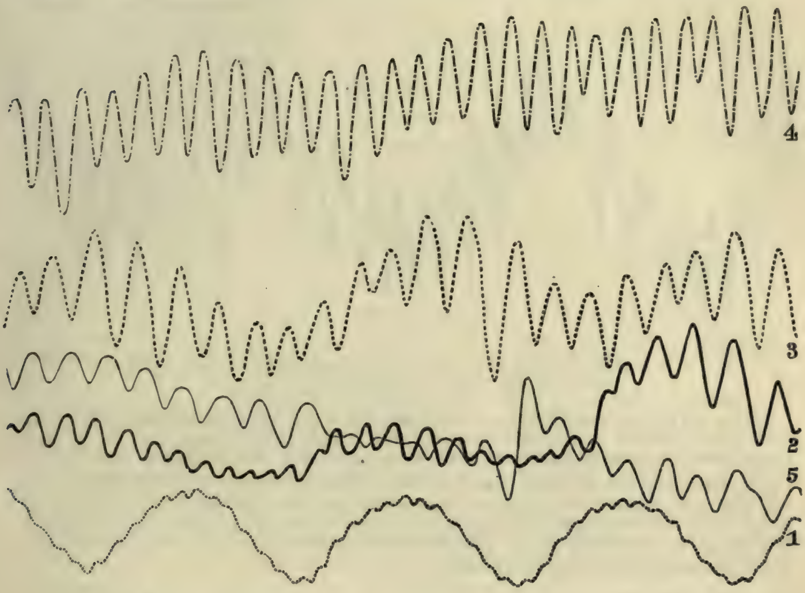

FIG. 86. BLOOD-PRESSURE CURVES DURING A SUSPENSION OF BREATHING. TRAUBE-HERING CURVES.

The curves 1, 2, 3, 4, 5 are portions selected from one long continuous tracing forming the record of a prolonged observation, so that the several curves represent successive stages of the same experiment. Each curve is placed in its proper position relative to the base line, which, to save space, is omitted; and it is obvious that, starting from the stage represented by 1, the blood-pressure rises in stages 2, 3, and 4, but falls again in stage 5. Curve 1 is taken from a period when artificial respiration was being kept up, and the undulations visible are those the nature of which have been discussed; the vagus nerves having been cut the pulsations on the ascent and descent of the undulations do not differ. When the artificial respiration was suspended these undulations disappeared, and the blood-pressure rose steadily while the heart-beats became slower. Soon, as shewn in curve 2, new undulations appeared. A little later, the blood-pressure was still rising, the heart-beats still slower, but the undulations still more obvious (curve 3). Still later (curve 4), the pressure was still higher, but the heart-beats were quicker, and the undulations flatter. The pressure then began to fall rapidly (curve 5), and continued to fall until some time later artificial respiration was resumed.

We may here incidentally remark that the occurrence of long slow undulations is not dependent on the cessation of the respiratory movements, and on an abnormally venous condition of the blood. They are sometimes (Fig. 87) seen in an animal whose breathing is fairly normal. We need not discuss them any further now, and have introduced them chiefly to illustrate the fact that the vaso-motor nervous system is apt to fall into a condition of rhythmic activity. It has been suggested that the normal respiratory undulations may be due to a rhythmic rise and fall of the activity of the vaso-motor centre, synchronous, like that of the cardio-inhibitory centre, with the respiratory movements.

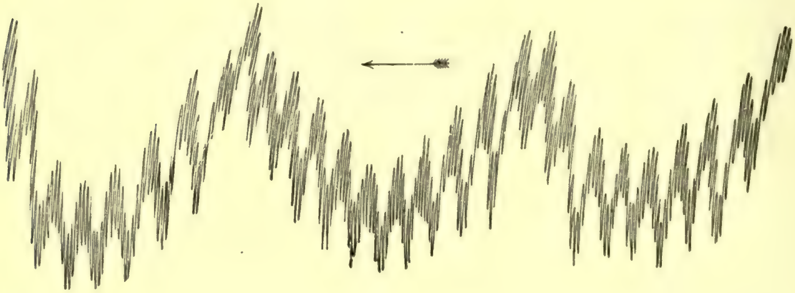

FIG. 87. BLOOD-PRESSURE CURVE OF A RABBIT, RECORDED ON A SLOWLY MOVING SURFACE, TO SHEW TRAUBE-HERING CURVES.

(The curve was described not by means of a mercury manometer, but by an instrument similar to but not identical with Fick's spring-kymograph.) In each heart-beat the upward and downward stroke are very close together but may be easily distinguished by the help of a lens. The undulations of the next order are those of respiration. The wider sweeps are the Traube-Hering curves, of which two complete curves and portions of two others are shewn. Each Traube-Hering curve comprises about nine respiratory curves, and each respiratory curve about the same number of heart-beats.

There can however be no doubt that the respiratory variations in blood-pressure are due to the mechanical conditions discussed above, and that vaso-motor influences intervene but little if at all.

§ **388**. The further general effects, similar to the above, on the vascular system of deficient arterialization of the blood may be studied by taking a blood-pressure tracing from the carotid or other artery of an animal while the interference with respiration is pushed on to a fatal asphyxia. During the first and second stages of the asphyxia the blood-pressure rises rapidly, attaining a height far above the normal. During the third stage it falls even more rapidly, repassing the normal and becoming *nil* as death ensues. If the animal, no urari having been given, is breathing of itself, and if, as usually is the case, the asphyxia is brought about by occlusion of the trachea, so that the mechanical effects of the respiratory movements are exaggerated by the air being unable to enter the chest, the respiratory undulations of the pressure-curve due to the mechanical causes discussed above are, especially during the first stage, extensive, abrupt and irregular, the inspiratory movements being accompanied by a conspicuous fall of pressure. When the animal has been previously placed under urari, so that the respiratory impulses cannot manifest themselves by any muscular movements, the rise of the pressure curve, as we have already said, is at first steady and unbroken, but after a variable period Traube's curves make their appearance. As during the third stage the pressure sinks, these undulations pass away.

The heart-beats are at first somewhat quickened, but speedily become slow, at the same time as we have seen not notably losing force, so that the pulse-curves on the tracing are exceedingly bold and striking. But the boldness of the curve of the mercury manometer, is, it must be remembered, partly the mere result of the slowness of the rhythm; the mercury has time to fall largely between each two beats (Fig. 86. 3 & 4). Even while the blood-pressure is sinking, and when the cardiac stroke is now certainly lessening in vigour, the slowness of the cardiac rhythm is still sufficient to maintain somewhat these characters of the curve. The strokes at last, however, rapidly fail in strength and become irregular, though the heart continues to beat for some seconds after the respiratory movements have ceased.

If the chest of an animal be opened under artificial respiration, and asphyxia brought on by cessation of the respiration, it will be seen that the heart during the second and third stages becomes completely gorged with venous blood, all the cavities as well as the large veins being distended to the utmost. If the heart be watched to the close of the events, it will be seen that the feebler strokes which come on towards the end of the third stage are quite unable to empty its cavities; and when the last beat has passed away its parts are still choked with blood. The veins spirt out when pricked: and it may frequently be observed that the beats recommence when the over-distension of the heart's cavities is relieved by puncture of the great vessels. When rigor mortis sets in after death by asphyxia, the left side of the heart is more or less emptied of its contents; but not so the right side. Hence in an ordinary post-mortem examination in cases of death by asphyxia, while the left side is found comparatively empty, the right appears gorged.

These various phenomena of asphyxia are probably brought about in the following way.

The increasingly venous character of the blood augments the action of the vaso-motor centres, both the medullary centre and the subsidiary centres in the spinal cord, and thus leads to a constriction of the small arteries, especially of the splanchnic area. This is the chief cause of the markedly increased blood-pressure; though the venous blood may possibly also act directly on peripheral vaso-motor mechanisms, or, what is more likely, may increase the peripheral resistance in the capillaries themselves, since there are reasons for thinking (§ 185) that venous blood rich in carbonic acid meets with more friction, and passes less easily through the capillaries than does blood less venous in character.

This increased peripheral resistance and the high blood-pressure to which it gives rise, while tending to increase the distension of the left ventricle and so indirectly helping to augment the force of the heart's beat, soon becomes a direct obstacle to the heart emptying itself of its contents. On the other hand, the laboured respiratory movements favour the flow of venous blood towards the heart, which in consequence becomes more and more full. This repletion is moreover assisted by the marked infrequency of the beats which is soon developed. This in turn depends in part on the cardio-inhibitory centre in the medulla being stimulated by the venous blood; but, as we have previously seen, cannot be wholly accounted for in this way. The increased resistance in front, the augmented supply from behind, and the long pauses between the strokes, all concur in distending the heart more and more.

When the large veins have become full of blood the inspiratory movements can no longer have their usual effect in facilitating the venous flow into the right auricle. The chief effect of the chest movement, as far as the circulation is concerned, is to widen and so to increase the capacity of the pulmonary vessels, and at the same time to diminish the pressure around the large arteries; hence the marked sinking of the blood-pressure during each inspiratory movement.

The distension of the cardiac cavities, at first favourable to the heart-beat, as it increases becomes injurious; and the cardiac tissues after a while become enfeebled by the action of the venous blood, so that the strokes of the heart become weaker and irregular.

On account of this increasing feebleness of the heart's beat, accompanied by more or less irregularity, the blood-pressure, in spite of the continued arterial constriction, begins to fall, since less and less blood is pumped into the arterial system; the boldness of the pulse-curves at this stage is chiefly due to the infrequency of the strokes. As the quantity which passes from the heart into the arteries becomes less second by second, the pressure gets lower and lower, the descent being assisted by the exhaustion of the vaso-motor centre, until almost before the last beats it has sunk to zero. Thus at the close of asphyxia, while the heart and venous system are distended with blood, the arterial system is less than normally full.

§ **389**. While changes occurring primarily in the respiratory system thus affect the vascular system, conversely changes occurring primarily in the vascular system affect the respiratory system. Two kinds of change in the vascular system bearing on two parts of the respiratory system deserve especial attention.

In the first place the respiratory mechanism may be affected by changes in the blood supply to the respiratory centre in the medulla. We have already seen (§ 371), that the sudden cutting off of the supply of blood to the medulla gives rise to dyspnœic respiratory movements and may lead to expiratory convulsions. That is an extreme case; but short of that, the activity of the respiratory centre, the extent and character of the respiratory explosions which take place in it, may be varied according as the constricted or dilated condition of the small arteries branching off from the basilar artery or of the basilar artery itself allows a scanty or a full flow of blood through the medulla. And it is possible that some forms of dyspnœa may be brought about in this way.

Much more common and important however is the second kind of change, that affecting the circulation through the lungs. In the normal organism an adequate supply of arterial blood to the tissues is secured by an adequate renewal of the air in the pulmonary alveoli and an adequately rapid flow of blood through the pulmonary capillaries. When, as by obstruction in the pulmonary arteries, or by failure of the cardiac valves, or, and perhaps especially, by an insufficient cardiac stroke, the stream of blood from the lungs into the left ventricle is lessened either in amount or in rapidity, less oxygen is carried to the tissues, including the nervous tissue of the medulla, and dyspnœa or "want of breath" follows. When the circulation through the lungs is in full healthy swing, the hæmoglobin of the red corpuscles is as we have seen saturated or nearly saturated with oxygen. If owing to a slower stream the red corpuscles tarry longer in their passage along the walls of the pulmonary alveoli they cannot thereby take up a compensating addition of oxygen, indeed it is doubtful if they can take up any additional oxygen at all. The blood falling under these circumstances into the left ventricle and sent thence over the body is not more arterial than usual; at the same time the amount of blood sent out at each heart stroke is less, often much less, than the normal; and the medulla as well as the other tissues suffer in consequence from a deficiency of oxygen. The deficient supply to the medulla manifests itself in dyspnœic or at least in laboured breathing, which sometimes through the mechanical influences discussed above has the happy result of improving the pulmonary circulation and so produces compensating effects. When the pulmonary artery is suddenly plugged with a clot the primary and urgent symptom is "want of breath," though air enters freely into the chest; and "cardiac dyspnœa" is a common symptom of cardiac disease.

§ **390**. Other systems of the body are also related to the respiratory system, though by ties less striking than those which bind to it the vascular system. We have seen that deficient arterialisation of the blood stirs up the muscles of the alimentary canal to increased activity, and we shall presently see that the same condition has a notable effect in promoting the perspiration;

it probably has a similar influence over other secretions. On the other hand, as we have seen § 373, there are reasons for thinking that the activity of the respiratory centre and so the energy of the whole respiratory act is influenced by chemical changes, other than the decrease of oxygen and increase of carbonic acid, brought about in the blood by the activity of the skeletal muscles.

The closeness and the intricacy of the ties which thus connect the respiratory system with almost all parts of the body may be illustrated by considering the effects of muscular work on the body, and the conditions which, apart from the capacity of the muscles themselves and of the motor nervous apparatus which puts them to work, determine the power of the body to do work. During work, especially arduous work, the muscular contractions rob the blood of much oxygen and load it with much carbonic acid. This change in the blood would itself increase the activity of the respiratory centre and the energy of the respiratory movements, and might be sufficient to secure such an increase of these movements that the deficiency of oxygen and increase of carbonic acid should never overstep certain limits. But, as we have said, apparently other products of muscular metabolism act so potently in stimulating the respiratory centre that the respiratory movements are more than sufficient to compensate the changes in the gases of the blood. The efficacy of the augmented respiratory movements is much increased by a concomitant increase in cardiac activity and a swifter or fuller stream of blood through the lungs; indeed unless backed up by the cardiac increase the mere increase of the pulmonary ventilation might prove inadequate.

Hence the capacity for arduous muscular labour is determined not by the respiratory mechanism alone, nor by the vascular system alone, but by both, and especially by both working together in harmony and concert. The increased ventilation would be idle unless it were accompanied by a quicker circulation, and the quicker circulation would similarly be of comparatively little use unless accompanied by increased ventilation. To a bystander the working of the respiratory pump is much more obvious than that of the vascular system, and indeed the subject himself is much more directly conscious of changes in the former than of changes in the latter. Hence when the organism ceases to be able to meet the demands which the labour is making upon it, the subject is said to be "out of breath," though in a large number of cases the failure lies much more at the door of the vascular than of the respiratory system. And, as a rule, it may perhaps be said that when two men differ in their capacity for strenuous work, such as running a race, the difference, though it is often familiarly spoken of as one of "wind" or power of breathing, is in reality not a difference in ventilating capacity but a difference in the power of the heart to keep up to and work in harmony with the increased respiratory movements.

Thus there are two main factors in respiration, the respiratory mechanism proper, and the circulation, the one bringing the air to the blood, and the other the blood to the air. We may remind the reader that there is also a third factor, and that one of great moment, the amount of hæmoglobin, that is, the number of red corpuscles, in the blood. The amount of oxygen taken up from the lungs depends not only on the strokes of the respiratory and the vascular pumps but also on the richness of the blood in red corpuscles. A body which from loss of blood or from disease is anæmic is thrown out of breath by very slight exertion, not so much because the respiratory or the vascular pump is weak, but because, through lack of oxygen carriers, with their best efforts the combined pumps can only deliver to the tissues, including the medulla, an inadequate supply of oxygen. And fat persons, whose store of hæmoglobin in proportion to their body weight is always below par, are proverbially "scant of breath."

SEC. 10. MODIFIED RESPIRATORY MOVEMENTS.

§ **391.** The respiratory mechanism with its adjuncts, in addition to its respiratory function, becomes of service, especially in the case of man, as a means of expressing emotions. The respiratory column of air, moreover, in its exit from the chest, is frequently made use of in a mechanical way to expel bodies from the upper air-passages. Hence arise a number of peculiarly modified and more or less complicated respiratory movements, sighing, coughing, laughter, &c. adapted to secure special ends which are not distinctly respiratory. They are all essentially reflex in character, the stimulus determining each movement, sometimes affecting a peripheral afferent nerve as in the case of coughing, sometimes working through the higher parts of the brain as in laughter and crying, sometimes possibly, as in yawning and sighing, acting on the respiratory centre itself. Like the simple respiratory act, they may with more or less success be carried out by a direct effort of the will.

Sighing is a deep and long-drawn inspiration, chiefly through the nose, followed by a somewhat shorter, but correspondingly large expiration.

Yawning is similarly a deep inspiration, deeper and longer continued than a sigh, drawn through the widely open mouth, and accompanied by a peculiar depression of the lower jaw and frequently by an elevation of the shoulders.

Hiccough consists in a sudden inspiratory contraction of the diaphragm, in the course of which the glottis suddenly closes, so that the further entrance of air into the chest is prevented, while the impulse of the column of air just entering, as it strikes upon the closed glottis, gives rise to a well-known accompanying sound. The afferent impulses of the reflex act are conveyed by the gastric branches of the vagus. The closure of the glottis is carried out by means of the inferior laryngeal nerve. See *Voice.*

In *sobbing* a series of similar convulsive inspirations follow each other slowly, the glottis being closed earlier than in the case of hiccough, so that little or no air enters into the chest.

Coughing consists in the first place of a deep and long-drawn inspiration by which the lungs are well filled with air. This is followed by a complete closure of the glottis, and then comes a sudden and forcible expiration, in the midst of which the glottis suddenly opens, and thus a blast of air is driven through the upper respiratory passages. The afferent impulses of this reflex act are in most cases, as when a foreign body is lodged in the larynx or by the side of the epiglottis, conveyed by the superior laryngeal nerve; but the movement may arise from stimuli applied to other afferent branches of the vagus, such as those supplying the bronchial passages and stomach and the auricular branch distributed to the *meatus externus.* Stimulation of other nerves also, such as those of the skin by a draught of cold air, may develope a cough.

In *sneezing* the general movement is essentially the same, except that the opening from the pharynx into the mouth is closed by the contraction of the anterior pillars of the fauces and the descent of the soft palate, so that the force of the blast is driven entirely through the nose. The afferent impulses here usually come from the nasal branches of the fifth. When sneezing however is produced by a bright light, the optic nerve would seem to be the afferent nerve.

Laughing consists essentially in an inspiration succeeded, not by one, but by a whole series, often long continued, of short spasmodic expirations, the glottis being freely open during the whole time, and the vocal cords being thrown into characteristic vibrations.

In *crying,* the respiratory movements are modified in the same way as in laughing; the rhythm and the accompanying facial expressions are however different, though laughing and crying frequently become indistinguishable.

CHAPTER III.

THE ELIMINATION OF WASTE PRODUCTS.

§ **392**. We have traced the food from the alimentary canal into the blood, and, did the state of our knowledge permit, the natural course of our study would be to trace the food from the blood into the tissues, and then to follow the products of the activity of the tissues back into the blood and so out of the body. This however we cannot as yet satisfactorily do; and it will be more convenient to study first the final products of the metabolism of the body, and the manner in which they are eliminated, and afterwards to return to the discussion of the intervening steps.

Our food consists of certain food-stuffs, viz. proteids, fats, and carbohydrates, of various salts, and of water. In their passage through the blood and tissues of the body, the proteids, fats and carbohydrates are converted into urea (or some closely allied body), carbonic acid and water, the nitrogen of the urea being furnished by the proteids alone. Many of the proteids contain sulphur, and also have phosphorus attached to them in some combination or other, and some of the fats taken as food contain phosphorus; these elements ultimately undergo oxidation into phosphates and sulphates, and leave the body in that form in company with the other salts.

Broadly speaking then, the waste products of the animal economy are urea, carbonic acid, salts and water. These leave the body by one or other of three main channels, the lungs, the skin, and the kidney. Some part, it is true, leaves the body by the bowels, for, as we have seen, the fæces contain, besides undigested portions of food, substances which have been secreted into the bowel, and are therefore waste products; but the amount of these is so small that they may be neglected.

The lungs serve as the channel for the discharge of the greater part of the carbonic acid, and a considerable quantity of water; this discharge we have just studied. Through the skin there leave the body a comparatively small quantity of salts, a little carbonic acid, and a variable but on the whole large quantity of water.

The kidneys discharge all or nearly all the urea and allied bodies, the greater portion of the salts, and a large amount of water, with an insignificant quantity of carbonic acid. They are especially important since by them practically all the nitrogenous waste leaves the body, and to them we will turn first.

SEC. 1. THE STRUCTURE OF THE KIDNEY.

§ 393. The kidney is a secreting gland constructed upon the general plan of a compound secreting gland, but possessing special features. The secreting portions, in which the divisions of the main duct or *ureter* end, are not relatively short tubes with branchings or lateral bulgings, that is to say, are not alveoli, but are extremely long narrow tubules, with no branchings or lateral bulgings. The whole body of the kidney is made up of these constituent tubules, uriniferous tubules, *tubuli uriniferi,* closely packed together with just as much connective tissue as is sufficient to carry a large supply of blood vessels, a certain number of lymphatics, and nerves.

Each uriniferous tubule, consisting of a single layer of epithelium resting on a basement membrane which over the great part of the length of the tubule is conspicuous and distinct, begins in a peculiar structure called a Malpighian capsule, and for the first part of its course pursues a path which is on the whole very twisted and devious, during which it may, for the present, be spoken of as a twisted tubule, corresponding to the *tubulus contortus* of old writers. It subsequently takes a more straight course, and is then called a straight tubule, *tubulus rectus.* At its beginning and during its twisted course, the tubule lies, for the most, near the surface of the kidney, forming the main part of the *cortex* of the kidney. During its straight course it runs towards the deeper parts, converging towards the concave border or hilus of the kidney where the main duct or ureter enters; the converging straight tubules forming together the *medulla* of the kidney. While pursuing the first twisted and devious part of their course, during the greater part of which as we shall see they possess marked secretory characters, the tubules do not join each other. During the latter straight part of their course, when as we shall see their characters are those of conducting rather than of secreting tubules, they repeatedly join. After each junction the tubule, though wider than each of the two tubules which joined to form it, occupies less space than the two together; hence the medullary substance becomes less as it converges towards the hilus. The medulla is moreover divided into a number (varying in different animals, being one in the rabbit and the rat, and about ten or twelve in man) of masses, each of which, since it diminishes in bulk towards the hilus, has the form of a pyramid, *pyramid of Malpighi*, with its apex directed radially towards the hilus and its base resting on and becoming confused with the cortex.

The *ureter* or main duct of the kidney when traced to the kidney, is found to expand at the hilus into a funnel-shaped cavity, the *pelvis*, which divides or branches somewhat irregularly into a number (equal to that of the pyramids) of short broad tubes, *calyces*, somewhat in the way that the hand of a glove divides into the fingers, but more irregularly. Into each calyx the summit of a corresponding pyramid projects for some little way in the form of a nipple, or *papilla*, the epithelium lining the calyx being thus continuous with, and as it were reflected to form the epithelium covering the projecting nipple of the pyramid. The straight tubules forming as we have seen the pyramid, though numerous at its base, become by repeated junctions fewer and larger, and finally form a number (in man about a score) of relatively wide tubules which open into the calyx at or near the very summit of the nipple; here the epithelium lining the tubules becomes continuous with the epithelium covering the papilla.

Hence in a radial section of human kidney (one taken in the long axis being preferable) the whole outer portion of the organ, all round except at the hilus, will be seen to be occupied by the fairly uniform cortex which, being composed as we have said mainly of tubes twisting in all directions, presents on section to the naked eye a granular aspect. From this cortex will be seen converging towards the hilus a certain number of pyramids, each of which since it is mainly composed of radiating straight tubules, and since the minute blood vessels ramifying in it have a similar radiating straight course, will present to the naked eye a more or less marked radiating grain or striation. The apex of each pyramid where the section has passed through the apex, will be seen projecting into its appropriate calyx, the calyces will be seen uniting to form the pelvis, and provided that the plane of section has passed through the mouth of the ureter, the pelvis will be seen narrowing into the ureter. The section may of course have missed the ureter; it is also very likely to have cut one or other of the pyramids higher up than the attachment of the calyx, in which case of course the projection of the papilla of the pyramid into its calyx is not seen.

The pyramids are separated from each other laterally, above the attachment of their respective calyces, partly by a small quantity of cortical substance which creeps down their sides towards the pelvis (columns of Bertini), and also by the larger branches of the blood vessels which, lying outside the pelvis, and dividing as it divides, plunge into the substance of the kidney between the calyces and so between the pyramids, and then run outwards towards the junction of the cortex and medulla to be distributed in a manner which we shall describe presently. The kidney is really, as is seen in the embryo kidney of man and indicated by the adult kidney of some animals, composed of lobes, each lobe consisting of a more central medulla in the form of a pyramid, covered especially at its base, but also to a certain extent at the sides by cortex, and opening at its apex into an appropriate division of the ureter. As in other glands the larger branches of the blood vessels run in the connective-tissue joining the lobes together, and pass thence into the lobes. In the adult kidney the lobes have become more or less fused together. In the cortex the fusion is complete, but the pyramids still maintain the medulla in a lobed condition, separated however laterally by nothing more than by blood vessels, with the connective-tissue carrying them, and a remnant of cortical substance. The surface of the kidney, save in abnormal cases, shews no indications of division into lobes; the uniform level of the cortex is bounded by a capsule of connective-tissue, which may be easily stripped off from the cortical substance below, and which at the hilus is continuous with the connective-tissue surrounding and binding together the ureter, renal vessels and renal nerves. A quantity of adipose tissue not infrequently surrounds the kidney, being especially abundant at the hilus.

§ **394**. Each tubule begins as we have said in a Malpighian capsule somewhere in the cortex, either near the capsule or near the base of a pyramid or at some intermediate level. From thence it runs, we have also said, first as a twisted tubule and subsequently as a straight tubule; but in the first part of its course its path is so peculiar that the word twisted does not accurately describe it. Moreover the characters of the tubule change so markedly at various parts of its course, and these changes are probably of such great importance, that a description of the tubule at successive steps of its progress along its whole length becomes advisable, though we at present do not understand the meaning of the various changes. As we shall see, some of these complex peculiarities of the mammalian kidney are partly explained by the structure of the kidney of one of the lower animals, such as a frog. It will be convenient to describe first some details of the general course, and to study the changes in character subsequently.

Leaving the capsule the tubule forms in the neighbouring cortex several sharp but rounded turns, and in this part of its course is very distinctly a twisted, contorted, *convoluted* tubule. It then, ceasing to be distinctly convoluted, takes on a wavy or gently spiral or sometimes almost straight course, being directed radially towards the medulla. In this part of its course it is spoken of as the *spiral* tubule. Still continuing its radial course, the tubule, suddenly diminishing very much in width, passes on for some distance right down into the pyramid below, until, at a level which differs with the different tubules but is always at some distance from the apex of the pyramid, the tubule bends sharply round, and pursues a backward nearly straight course, parallel to its former one, until it finds itself back again in the cortex at some distance from the medulla; the tubule in fact, in continuation of the spiral segment, makes a loop, *the loop of Henle*, dipping down into the medulla for a certain distance, and consisting of a *descending* and an *ascending limb*, both of them running a radial course which is straight or nearly so. The descending limb is as we have said very narrow, but either before it makes the bend, or just at the bend, or at some little distance beyond the bend when it has already become the ascending limb, it enlarges somewhat and changes in character though not reaching the diameter of the spiral or convoluted tubule. Having reached some part or other of the cortex, in a more or less straight radial line, the ascending limb of the loop of Henle changes again in character, becomes still wider, and runs in the cortex a once more distinctly twisted course; the twists however are not round but angular, giving the tubule a zigzag appearance; hence this portion of the tubule is called the zigzag or sometimes the *irregular* tubule. Very soon however the turns of the tubule become rounded, and the tubule still running in the cortex assumes characters almost identical with those of the initial convoluted portion; it now receives the name of the *second convoluted* tubule. After several turns of this kind, all confined to the cortex, the tubule once more changes in character and, running a second time in a straight radial course towards the medulla, becomes a *collecting* tubule pursuing a straight radial course directed towards the apex of a pyramid. The collecting tubule, joining other collecting tubules, and changing slightly in character, while by repeated junctions becoming larger, is continued on as a *discharging* tubule which, joining other tubules as it passes towards the apex of the pyramids, opens at last into a calyx at or near the summit of the papilla of the pyramid.

Thus each tubule starting from a Malpighian capsule becomes in succession a first convoluted tubule, a spiral tubule, a descending and ascending limb of a loop of Henle, a zigzag or irregular tubule, a second convoluted tubule, a collecting tubule and finally a discharging tubule. The discharging portion, the lower part of the collecting portion, and some part or other of the loop of Henle lie in the medulla, and form part of one or other of the pyramids. In all the rest of its course the tubule lies in the cortex; but from what has been said it is obvious that the part of the tubule confined to the cortex can not be called, along the whole length of its course, a twisted or contorted tubule. The upper part of the collecting tubule though still lying in the cortex runs nearly straight; the beginning of the descending limb and the end of the ascending limb of the loop of Henle though lying in the cortex are nearly straight; and even the spiral tubule is not far removed from being straight. So that the cortex does not consist of convoluted tubules only but in part of tubules more or less straight. These however are not dispersed uniformly among the convoluted tubules, but are gathered into bundles which run in a radial direction from the bases of the pyramids through the cortex towards the capsule. The bundles, of which there are several to each pyramid, are called *medullary rays* or *pyramids of Ferrein* (the large pyramids of the medulla being then distinguished as the pyramids of Malpighi).

Between and surrounding the several medullary rays are masses of cortex, seen in radial sections as columns between two adjacent rays, consisting of convoluted tubules, both first and second, of zigzag tubules, and as we shall see of Malpighian capsules; all the tubules in the column are most distinctly twisted and contorted, since the column contains only the very beginnings of the spiral tubule, and the collecting tubule. The spiral tubule beginning in the column of cortex between the medullary rays makes at once for a medullary ray down which it runs to become a descending limb of the loop of Henle; the ascending limb coming up from the medulla runs in a medullary ray and only leaves it to become a zigzag tubule; and each collecting tubule runs straight into a medullary ray and thence away into the medulla. Hence each ray consists of spiral tubules, descending and ascending limbs (especially the latter) of the loops of Henle, and collecting tubules.

Since each medullary ray receives spiral tubules and collecting tubules, and gives off zigzag tubules at different levels above the bases of the pyramids, it must be thicker below, where it holds all the tubules which it has received or is about to give off, than higher up, where it has already given off some tubules and has not yet received all the tubules which it will receive. It diminishes in fact, pyramid fashion (hence the name pyramid of Ferrein), towards the surface of the kidney; and indeed just below the capsule there is a layer of some little thickness consisting entirely of cortical substance, that is of convoluted tubules, the medullary rays not having as yet begun.

It is obvious that the upper part of each pyramid of the medulla differs from the lower part, in so far as that while the latter contains straight tubules only, and these mostly discharging tubules, the former contains, besides collecting and discharging tubules, the ends of the loops of Henle, which are really parts of the tubules in what we have called generally their twisted, or devious course. Hence the upper part of the medulla contiguous to the cortex is sometimes spoken of as the *boundary zone* or *intermediate zone*.

§ **395**. Having thus traced out the devious and complex path taken by a tubule we must study in more detail the special characters of the several sections of its course.

The Malpighian Capsule. Each tubule begins as we have said in a globular expansion, having in man a diameter of about 200μ, the Malpighian capsule or end-capsule. The several capsules are disposed for the most part in series of circles around the medullary rays along their length, so that in radial sections of a kidney they are seen in double radiating rows in the columns of cortical substance between the medullary rays. Each capsule is essentially a terminal globular expansion of a tubule, and consists, like the tubule, of a distinct and conspicuous basement membrane, having the ordinary characters of a basement membrane (§ 211), lined by an epithelium. At one pole of the sphere the capsule is continued on into the tubule, its basement membrane and its epithelium being continuous with the basement membrane and the epithelium of the tubule; at the junction of the two there is a marked constriction or neck. At the opposite pole a short straight small artery (of whose relations we will speak presently), *vas afferens*, runs into the capsule, driving before it and inverting into the cavity of the capsule the basement membrane and epithelium somewhat in the way that one might thrust one's fist into and so invert at one part the wall of a large distended elastic ball. Immediately upon its entrance into the capsule the afferent artery divides into a number of branches. Each branch further splits up into a number of capillary loops, the returning limbs of the several loops joining, without lateral anastomoses, to form a single vein-like vessel, *vas efferens*. The whole lobulated bunch of branching and looped vessels has more or less the appearance of a knot, and is called the *glomerulus*. The exact mode of division however differs in different animals and apparently in different capsules in the same kidney; thus in the capsules nearer the medulla the glomeruli are larger and more subdivided than in those nearer the surface. The vas efferens starting from about the middle of the bunch issues from the capsule side by side with the vas afferens, the orifice formed by the inversion of the capsule being not wide but narrow so as just to admit the entering and issuing vessels. Hence the glomerulus hangs as it were into the cavity of the capsule suspended by a narrow neck consisting of the afferent and the efferent vessel, surrounded by the commencement of the inverted portion of the wall of the capsule. When the blood vessels are fully distended with blood the glomerulus fills the greater part of the cavity of the capsule; when they are constricted and contain little blood, a space of some size is developed between the surface of the glomerulus and the opposite wall of the capsule.

The epithelium lining the wall of the capsule consists of flat polygonal nucleated cells which have almost an epithelioid character. Indeed they are seen with difficulty and are best brought into view by the silver nitrate method. These cells rest on a basement membrane which as we have said is distinct, and in optical or other section presents a sharp outline.

The basement membrane over the glomerulus cannot be so readily distinguished. It appears to be completely fused with the wall of the capillary loops, which like other capillaries consist of a homogeneous membrane of nucleated epithelioid plates cemented together. The epithelium covering the glomerulus, which follows the inequalities of the surface, forming a covering for and dipping down between the groups of capillary loops, and hence is in close contact with the blood vessels, is said to differ from the epithelium lining the wall of the capsule inasmuch as the cells do not so closely resemble epithelioid plates, but are flattened cells, often irregular in form, each with a transparent or faintly granular cell-substance and rounded nucleus; they are distinctly cubical in the new-born animal but become flatter in the adult. Thus each of the capillary loops of the glomerulus appears to project into the cavity of the capsule in such a way that the blood in the vessel is separated from the cavity of the capsule, and so from the lumen of the tubule, first by a thin film composed of the capillary wall (with which the basement membrane of the inverted portion of the capsule has become fused), and next by an epithelium cell of somewhat peculiar nature. As we shall presently see some of the problems concerning the secretion of urine turn on the nature of the processes carried out by this film covered with this epithelium.

Each capsule is surrounded by a small quantity of connective-tissue which, very scarce in the kidney generally, is more obvious here than elsewhere. A small amount of connective-tissue also surrounds the afferent and the efferent vessel of the glomerulus, but a minimum of this tissue is carried into the capsule with the glomerulus. Indeed the presence of connective-tissue to form a middle to or a support of a loop or even in the depths of the glomerulus, cannot be definitely demonstrated. Hence, though we have reason to think that lymphatics exist in the tissue around the capsule as elsewhere in the kidney, it has been maintained that lymphatics are absent in the glomerulus between the blood vessels. In at all events the peripheral portion of each capillary loop, covered as it seems to be closely by epithelium, the only exit of material through the capillary wall leads direct through the epithelium into the cavity of the capsule.

The capsule is continued on into a tubule by a short constricted portion or neck; and here the epithelium suddenly changes in character and puts on the features which we are now about to describe.

In the *first convoluted tubule* the basement membrane is distinct and conspicuous; indeed we may say at once that this distinctness and sharpness of outline of the basement membrane holds good for the whole length of the *tubulus uriniferus* until we reach the discharging tubules in the medulla; and here the basement membrane is lost to view simply because it becomes fused with the connective-tissue groundwork or stroma which is especially well developed in the lower part of a pyramid. Elsewhere the basement membrane may easily be recognized as an independent membrane.

The epithelium of the first convoluted tubule has the following characters. The outlines of the cells are very indistinct, so that not unfrequently the tubule seems to be lined by a layer of cell-substance in which rounded nuclei are imbedded at intervals. When the outlines are made out it is seen that each cell, which has a rounded nucleus placed at about its middle, is more or less cubical, sometimes of such a height as to leave a narrow, sometimes so low as to leave a fairly wide lumen. The outer portion of the cell next to the basement membrane is in many specimens striated radially; the appearance suggests that the cell substance is here composed of prisms or rods stretching radially from the basement membrane to or beyond the region of the nucleus and united together by some substance of a different nature; but in many good specimens such a striation may be absent or indistinct. The inner portion of the cell, next to the lumen, is of a more ordinary granular appearance, but the free border is frequently jagged, bearing irregular processes projecting into the lumen, and having somewhat the appearance of broken cilia, though they are not of the nature of cilia. In the frog and some other animals the first portion of the urinary tubule bears long, active cilia; but, as we shall see, this ciliated portion corresponds to the short constricted neck of the tubule in the mammal, and is succeeded by a non-ciliated portion which corresponds to the portion which we are now describing. The whole cell stains readily and deeply with the ordinary staining reagents. It may contain fat globules arranged in rows, leaving spaces or vacuoles when the fat is removed; sometimes these are very numerous. The appearances in fact presented by the cells in this first part of the tubule differ very much in different specimens; but we have at present no exact knowledge which will enable us to correlate any of these differences to functional activity.

The *spiral tubule,* which is as wide as or even wider than the convoluted tubule, possesses a wide and regular lumen. The cells which line the tubule have much the same character as in the convoluted, but are lower and more regular in form; hence the wider and more regular lumen; their striation also is less distinct and may be absent. The rounded nuclei of the cells are very conspicuous.

The *descending limb of the loop of Henle* into which, as it passes down the medullary ray, the spiral tubule suddenly changes, is very unlike all the rest of the tubule, and presents special features which call to mind those of a ductule of a salivary or pancreatic alveolus. It is very narrow, 10 to 15μ, and the cells which line it are somewhat oval cells placed lengthwise, each with an oval nucleus also placed lengthwise, and a clear cell-substance which is thicker round the nucleus than elsewhere. In a longitudinal section of the tubule, optical or other, the cell appears spindle-shaped with the part round the nucleus projecting into the lumen; the projections thus formed on one side of the tubule alternate with those on the other side so that the lumen winds in a wavy course between the projections. A transverse section shews corresponding bulgings of the cells into the lumen. Hence this part of a tubule is not wholly unlike a capillary, but may be distinguished by being somewhat larger, by having a basement membrane distinct from the cells, and by the cells, though clear in comparison with other parts of the tubule, being not so transparent as and staining more readily than the epithelioid plates of a capillary.

The *ascending limb* over the greater part of its course presents very different characters, the exact point at which the change takes place varying, as we have said, a good deal. The tubule is now wider, 30μ, but not so wide as the convoluted tubule. The cells, which leave a narrow but regular lumen, vary a good deal in form but are composed of cell-substance which always stains deeply, and which in its outer part is frequently striated. Very commonly the cells as seen in a longitudinal section of the tubule overlap each other so as to present an imbricated thatched appearance; the nuclei are usually oval.

The *irregular or zigzag tubule,* in which the ascending limb, running up the medullary ray and leaving the ray at one or other level to plunge into the cortex, ends, is a wide tubule which takes a course bending on itself several times at somewhat sharp angles. The cells are irregular in form, with nuclei which also appear to be irregular, stain very deeply with the staining reagents, and are often conspicuously striated in their outer part; the lumen is very irregular. This part of the tubule may perhaps be considered as an enlarged ascending limb with exaggerated features.

The *second convoluted tubule* so exactly repeats the features of the first convoluted tubule that the description given for that may be applied to this.

The *collecting tubule,* in which the second convoluted tubule making its way once more to the medullary ray ends, is a narrow tubule with a relatively wide lumen. The cells which line it are low short cubical cells, with small rounded nuclei and clear transparent cell-substance. They stain much less readily than the cells in any of the preceding parts of the tubule, even in the descending limb, and hence in properly stained specimens can be easily distinguished.

The *discharging tubule,* in which the collecting tubule passing straight down into the pyramid ends after several junctions with its fellows, has much the same characters as the collecting tubule, save that it becomes increasingly larger, and the cells lining it are taller and more columnar.

At the mouth of the ultimate discharging tubules as they open on the papilla of a pyramid, the single layer of columnar or cubical cells lining the tubule becomes continuous with the epithelium coating the papilla; and this, like the epithelium lining the calyces, pelvis and ureter, consists of two or three layers of cells of whose characters we shall speak later on.

§ **396**. Bearing in mind what we have previously learnt concerning secreting epithelium in other glands, it is obvious that the cells of the convoluted and irregular tubules are cells which exhibit to an eminent degree the characters of active secreting cells. The same may be said, though less emphatically, of the cells of the spiral tubule, and of the ascending limb of the loop of Henle. The cells of the collecting and discharging tubules on the other hand possess those characters which we associate with cells lining the conducting portions of a gland; but in saying this we may repeat the caution § 240, that we must not assume that the cells in such a situation do nothing else than afford a smooth lining for the passage of material secreted elsewhere.

The cells of the descending limb of the loop of Henle are peculiar; they are certainly conducting rather than secreting cells; but the meaning of this remarkable loop of Henle is at present obscure. Its presence in the mammalian kidney is in part but only in part explained by the characters of the urinary tubule in the lower animals. In the frog, newt and other amphibia the tubule begins as in the mammal, in a Malpighian capsule, and the first part of the tubule succeeding the Malpighian capsule is lined by clear cells leaving a narrow lumen into which project from the cells remarkably long cilia directed downwards and moving, in the living kidney, with an undulatory movement. This first part is obviously a conducting part, and is represented in the mammalian kidney by nothing more than the constricted neck which joins the capsule to the convoluted tubule; we may speak of it as the first conducting portion. The succeeding part is a wider tube lined by cells which bear no cilia, but whose free border is beset by short, rigid narrow processes, like short bristles. This is obviously a secreting portion, and we may speak of it as the first secreting portion; it corresponds to the first convoluted and the spiral tubule of the mammalian kidney, though the cell-substance is not striated as in the mammal. There next follows a section in which the tubule is of much narrower diameter and the cells, formed of clear cell-substance, again bear long cilia, constituting a second conducting portion. This second conducting ciliated portion is in turn succeeded by a division of much larger diameter in which the cells are most distinctly striated and otherwise resemble the cells of the convoluted tubules of the mammalian kidney, thus constituting the second secreting portion. The succeeding portions of the tubule have the character of conducting tubules, and join their fellows to fall ultimately into the ureter. Obviously the second secreting portion is represented in the mammal by the second convoluted tubule, the zigzag tubule and the ascending limb of Henle's loop, while the descending limb of Henle's loop corresponds to the second conducting ciliated portion of the amphibian tubule; the cilia however have entirely disappeared, and the likeness is confined to the narrowness of the whole tubule and the absence of secreting characters in the cells. Why however the kidney of the lower animal possesses this reduplication of secreting and conducting portions, and why remains and remains only of the reduplication should thus be preserved in the mammalian kidney, has not yet been satisfactorily explained.

§ **397**. The vascular arrangements of the kidney deserve special attention. The renal artery approaching the kidney at the hilus divides into branches which slipping round the pelvis enter into the substance of the kidney at the angles formed by the branching of the pelvis into calyces, and therefore between the pyramids. Running radially between the pyramids the branches, reaching the boundary between cortex and medulla, divide and, spreading laterally, form at the bases of the pyramids arches more or less concentric with the hilus. From these arches, which anastomose to a certain extent with other, vessels proceed on the one hand to the cortex and on the other to the medulla.

To the cortex are given off relatively large arteries which run in a radial direction towards the surface in the masses of cortex between the medullary rays. From each of these *interlobular* or *radiate arteries* as they are called, short relatively thick branches are given off at intervals on all sides; these taking a course somewhat curved, with the convexity directed towards the surface of the kidney, end, without branching, in Malpighian capsules; they are the afferent vessels spoken of previously. Other branches of the same radiate arteries break up into capillaries surrounding the tubules, this being especially the case near the surface of the kidney. The efferent vessels from the Malpighian capsules also break up into a capillary network which, embracing the tubules, becomes continuous with the other network, the meshes being rounded or polygonal in the cortical substance, but more elongated radially in the medullary rays. The blood-supply here repeats on a small scale the portal system of the liver, since a vessel formed by the union of capillaries breaks up in capillaries once more.

From the same arterial arches at the boundary of the cortex and medulla branches are also given off to the medulla, that is to say to the pyramids. These running in a straight or rather radial direction down the pyramids, as *arteriæ rectæ,* but soon breaking up into bundles of smaller vessels also running radially, supply all the medullary substance of the pyramids with blood, forming capillary networks with meshes elongated radially.

From the capillaries of the pyramids veins are gathered up, and these running radially upwards fall into venous arches, which, like to and even better developed than the arterial arches, are placed at the boundary between the cortex and medulla. Following reversely the course of the arteries these venous arches, forming more numerous anastomoses than do the arteries, fall into veins which running radially between the pyramids join together over the pelvis of the kidney and form eventually the renal vein; this, running in company with the renal artery, falls into the vena cava inferior.

From the capillaries of the cortex, including the medullary rays, the blood, some of which as we have seen has passed through the glomeruli of the Malpighian capsules, but some of which has not, is gathered up into radiate veins which running radially inwards to the boundary zone fall into the venous arches spoken of above. At the surface of the cortex the small veins are apt to be arranged in a somewhat star-shaped fashion, and are spoken of as *venæ stellatæ.*

Relatively to the bulk of the kidney the renal artery has large dimensions. Coming off directly from the aorta, where the blood-pressure is very high, and being comparatively short, it affords favourable conditions for an ample supply of blood to the organ, the conditions being made still more favourable by the low pressure existing in the vena cava inferior. And, as a matter of fact, the blood-supply to the kidney is very large. That blood is carried, as we have seen, in the first instance almost straight to the boundary of cortex and medulla, and is distributed from that region. Hence it results that the blood-supply of the pyramids consisting chiefly of conducting tubules is to a very large extent distinct from that of the cortex where the tubules are chiefly secreting tubules.

We may repeat that for its size the kidney is most abundantly supplied with blood. In sections of hardened and prepared kidneys, the arteries, capillaries, and to a large extent the veins are emptied of their blood, and the capillaries collapsed. Hence, judging by such specimens alone, the kidney appears to be made up almost of tubules alone; but it must be borne in mind that during life every tubule is netted round with fairly close-set capillaries which always are more or less filled with blood, and at times largely distended with blood. As we shall see later on, the kidney by mere decrease or increase of the blood flowing through it may vary very widely in volume.

§ **398**. The connective-tissue which binds together the tubules and blood vessels is exceedingly scanty. Some small amount enters with the blood vessels, and is continued on along their larger branches, but in the cortex the "stroma" consists of hardly more than the basement membranes of the tubules, with a few connective-tissue corpuscles imbedded in a scanty homogeneous not fibrillated matrix lying between them; around the capsules this stroma is rather more abundant than elsewhere, and here is sometimes fibrillated. In the pyramids, especially at their lower parts, a larger amount of a similar homogeneous matrix, containing connective-tissue corpuscles, is found between the tubules; and since here the basement membrane of the tubule is fused with this stroma, the tubule appears as a tubular cavity hollowed out of the matrix or stroma and lined with epithelium.

The whole kidney is surrounded by a capsule, consisting of ordinary connective-tissue and continuous at the hilus with the connective-tissue forming the outer walls of the pelvis and ureter. This capsule may after death be peeled off, and slender processes of connective-tissue with some blood vessels passing from the capsule into the cortex are then disclosed.

In the scanty stroma are numerous lymph-spaces, the lymph from these being collected into lymphatic vessels which in part leave the kidney by the hilus together with the blood vessels, and in part run in the capsule and leave the kidney on its convex surface. The capsule is described as separable into two layers, and the lymphatic vessels run chiefly between these layers.

§ **399**. As the renal artery passes to the kidney it is invested by a number of (twenty or less, in the dog a dozen or more) nerves, arranged in a plexus, the *renal plexus*. The nerves are composed partly of medullated fibres of very different sizes and partly of non-medullated fibres; numerous small ganglia, differing however very much in size, are scattered over the plexus.

The nerves thus forming the renal plexus come chiefly from the great solar plexus, and appear to be more immediately connected with the part of that plexus which is called the semilunar ganglion. The plexus is therefore indirectly connected with the nerves entering into the solar plexus, such as the right vagus and the abdominal splanchnic nerves, great and small. Besides this the splanchnic nerves appear to send filaments directly to the renal plexus; filaments have also been traced to the left kidney from the left vagus (which does not join the solar plexus), and it is contended that filaments from the right vagus also make their way direct to the right kidney, without distinctly communicating with the solar plexus.

As we shall see there is experimental evidence that, in the dog, nerve fibres from the anterior roots of the 11th, 12th and 13th dorsal spinal nerves and even a few fibres from still lower nerves find their way to the renal plexus and so to the kidney.

These make their way from the sympathetic chain, into which they first pass either by joining the splanchnic nerves low down, or by a more direct course, to the solar plexus, and thence to the renal plexus.

Nothing very definite is known of the termination of the renal nerves within the kidney. Some of them, and considering how vascular is the kidney, probably a large number, end in the blood vessels; but some of them must have other endings. We have, however, no evidence that any of them are connected with the epithelium of the tubules. Since under abnormal circumstances afferent impulses sufficient to give rise to very great pain may pass up to the central nervous system from the kidney, at least from the pelvis of the kidney, some of the fibres of the renal nerves are afferent fibres; and some of the medullated fibres are probably of this nature.

SEC. 2. THE COMPOSITION AND CHARACTERS OF URINE.

§ 400. These are so fully dwelt upon in special works that we may confine ourselves here to salient points. The healthy urine of man is a clear yellowish slightly fluorescent fluid, of a peculiar odour, saline taste, and acid reaction, having a mean specific gravity of 1·020, and generally holding in suspension a little mucus. The mucus, when present, comes from the urinary passages, as do also the occasional epithelial cells. All the rest of the urine may be considered as the secretion of the kidney.

The urine as we have said is the chief channel by which solid matters leave the body, a small quantity only passing by the skin and practically none by the lungs. Hence, neglecting for the present the skin, we may say that all the substances taken into the body sooner or later leave the body by the urine, save the few substances which may be retained permanently within the body and the substances which make up the body at the moment of its death. We accordingly find that the urine contains a large number of substances, the exact amount of each substance present in a given quantity of urine varying, in the case of every substance somewhat, and in the cases of many substances very largely, from time to time. The composition of urine is not only complex but extremely variable.

Moreover a little consideration will shew that the several substances present in urine must have very different histories. Some of the constituents of urine appear in it in the exact form in which they were introduced into the mouth; they have been simply absorbed from the alimentary canal into the blood and excreted by the kidney without undergoing change; they are derived directly and without change from the food.

Others again are the products of changes which the food has undergone in the body; and these changes may be slight or may be extensive, and may take place on the one hand in the alimentary canal, or during a brief transit of the substance in the blood-stream, or even in the urine itself, may so to speak be superficial;

or on the other hand may take place in the very depths of the tissues and be closely associated with the very life of the tissues. We shall, however, have to return to these matters later on, and may here briefly consider what substances are, normally and abnormally, present in urine, and the chief features of the fluid itself.

§ **401.** Besides *water*, the constituents of urine are:—

Nitrogenous Crystalline Bodies. Neglecting the small proportion of these bodies which, especially in the case of flesh eaters, are introduced into the economy with the food, as kreatin and the like, and so pass into the urine with no or with comparatively little change, we may on the whole regard the substances of this class as the products of the changes which the proteid matters (and allied substances such as gelatin and the like) present in food have undergone either while the food was simply food, still in the alimentary canal for instance, or after the food had been built up into the tissues of the body.

Of these by far the most important, in the urine of man and mammalia, is the body *urea* (N_2H_4CO). It is the chief form in which, in these animals, nitrogen leaves the body. We shall have to discuss the relations and formation of urea later on, but meanwhile we will simply state that it has remarkable double connections with two great groups. On the one hand it is related to the ammonia group, and by hydration is readily converted into ammonium carbonate ($N_2H_4CO + 2H_2O = (NH_4)_2CO_3$). On the other hand it is related to the great cyanogen group, ammonium cyanate and urea being isomeric, and the former by simple heating being converted into the latter ($NH_4 . CNO = N_2H_4CO$).

Though a base, forming salts with acids, such as nitrates, oxalates, &c. urea occurs in urine in a free and independent condition.

Closely allied to urea, occurring apparently as a bye product of the same line of metabolism, is *uric acid* ($C_5H_4N_4O_3$), which is found always in the urine of man, occurring in small but variable quantity. In the urine of some animals such as birds and reptiles it occurs in abundance, and indeed in these replaces urea as the chief nitrogenous excretion. Uric acid is a more complex body than urea, one molecule of uric acid splitting up, under the influence of certain reagents, into two molecules of urea and a compound of oxalic acid. Its decomposition products however, under different reagents, are very numerous and complex though urea occurs among them frequently and characteristically. Uric acid may be synthetically produced out of urea and glycin (glycocoll).

It is a weak dibasic acid, and occurs in normal human urine, not as a free acid but as an acid salt, being combined with potassium and sodium, and to a less extent with calcium and ammonium. In quite normal urine these salts are soluble in the urine, even after the fluid has cooled down to the ordinary temperature of the air; but not infrequently the urates, soluble in the urine at the temperature at which it leaves the body, are precipitated when the fluid cools, forming the well known "deposit of urates." On further standing the salts are apt to be decomposed and thus to give rise to crystals of uric acid.

Besides urea and uric acid the urine contains small but variable quantities of more or less nearly allied bodies such as kreatinin, xanthin, hypoxanthin, and guanin. Concerning these we will at present only say that kreatinin is a hydrated form of the body kreatin which we spoke of (§ 62) as a constituent of muscles. Kreatin by hydration is readily converted into kreatinin, and kreatinin by dehydration into kreatin; kreatin introduced into the alimentary canal or into the blood appears in the urine as kreatinin; and in flesh eaters some at least of the kreatinin of the urine is derived directly from the kreatin present in the meat eaten as food; but we shall discuss the subject of kreatin later on.

Besides the above, such bodies as leucin, taurin, cystin, allantoin and ammonium oxalurate are occasionally found in urine, but cannot be regarded as constituents of normal urine.

In the urine of man *hippuric* acid appears to be always present in small quantities, and in the urine of herbivora occurs in large quantities. In these latter it is derived more or less directly, by changes of which we shall have to speak in a succeeding chapter, from constituents of the food containing bodies belonging to the aromatic group (benzoic acid series); but the small quantity present in man and other carnivora appears to come from the metabolism of proteid matter which, as we have already seen, contains an aromatic constituent. Another member of the aromatic group, tyrosin, is occasionally present in urine; and as more regular constituents of normal urine may be mentioned certain phenol compounds, such as phenylsulphuric acid, the phenol constituents of which are derived from the action of micro-organisms in the alimentary canal, see § 282; these substances though they no longer contain nitrogen take origin from bodies of the aromatic series. Similar changes are also the source of indigo compounds (indican) in the urine, derived from indol, see § 249.

§ **402.** *Inorganic Salts.* These for the most part exist in urine in natural solution, the composition of the ash almost exactly corresponding with the results of the direct analysis of the fluid; in this respect urine contrasts forcibly with blood, the ash of which is largely composed of inorganic substances, which previous to the incineration existed in peculiar combination with proteid and other complex bodies. In the ash of urine there is rather more sulphur than corresponds to the sulphuric acid directly determined; this indicates the existence in urine of some sulphur-holding complex body. And there are traces of iron, pointing to some similar iron-holding substance. But otherwise, all the substances found in the ash exist as salts in the natural fluid.

The chief bases are sodium, potassium, calcium and magnesium in the form of chlorides, phosphates and sulphates. The exact way in which the several bases and acids are combined is to some extent a matter of uncertainty; but sodium chloride is certainly present and in considerable quantity; it is the most abundant and important inorganic constituent. A large portion of the phosphoric acid seems to exist as acid sodium phosphate, the rest as soluble calcium and magnesium phosphates. The remaining chief salts, occurring however in smaller quantity, are potassium and sodium sulphate, and calcium chloride.

Ammonia occurs in small quantity, alkaline carbonates are frequently found, traces of nitrates are at all events occasionally present, as also indications of silicates and of sulpho-cyanates.

The phosphates are derived partly from the phosphates taken as such in food, partly from the phosphorus or phosphates peculiarly associated with the proteids, and partly from the phosphorus of certain complex fats such as lecithin. When urine becomes alkaline (and, as we shall presently see, it may do so by changes taking place in itself) the calcic and magnesic phosphates are converted into basic salts which, being insoluble, are precipitated, the sodium phosphate remaining in solution. When the alkalinity, as is frequently the case, is due to ammonia, ammonio-magnesium phosphate is formed and is apt to appear in crystals. The sulphates are derived partly from the sulphates taken as such in food and partly from the sulphur of the proteids. The carbonates, when occurring in large quantity, generally have their origin in the oxidation of such salts as citrates, tartrates, &c. The bases present depend largely on the nature of the food taken. Thus with a vegetable diet, the excess of the alkalis in the food reappears in the urine; with an animal diet, the earthy bases in a similar way come to the front.

§ **403**. *Non-nitrogenous Bodies.* These exist in very small quantities, and many of them are probably of uncertain occurrence. Some of these are organic acids, the most constant perhaps being oxalic acid; to this may be added glycerin-phosphoric, lactic, formic, acetic, butyric and possibly succinic acids. Inosit has also been said to occur normally. It has been maintained that minute quantities of sugar (dextrose) are invariably present in even healthy urine; this however has not as yet been placed beyond all doubt. The nature of the substances which give to urine its characteristic odour has not been made out; probably there are more such bodies than one.

§ **404**. *Pigments.* Urine is always coloured, the tint varying from a light to a dark yellow with an admixture of brown. In the course of twenty-four hours, a not inconsiderable quantity of pigment must leave the body by the urine; but the nature of the normal pigment or pigments of urine is at present obscure and the subject of much controversy. The matter is apparently further complicated by the presence in urine of what have been called 'chromogens,' that is to say, bodies which are not coloured themselves but which readily give rise to pigments upon oxidation; and it is probable that some of these 'chromogens' of the urine are reduction products of the respective pigments, the reduction taking place in the urine after secretion, or during or even before secretion. There is frequently present in urine, especially in cases of fever, a pigment which has been isolated and determined, which has a characteristic spectrum, and which being maintained by some to be a derivative of bilirubin, has been called *urobilin.* It is not this urobilin however which gives to urine its ordinary colour. Some observers, on the other hand, maintain that normal urine does contain and, in part at least, owes its normal colour to a somewhat similar but different body, which in consequence they have called 'normal' urobilin. It is in fact not possible, at the present moment, to make definite and satisfactory statements as to whether urine contains one or more than one normal pigment, as to its or their nature, as to whether they are derived from bile-pigment or directly from the hæmatin of hæmoglobin or in other ways, or as to the several steps by which they are produced. There are also abnormal colouring matters present on occasion, such for instance as the peculiar red colouring matter occurring sometimes in the urine of acute rheumatism, which has been called uroerythrin; but our knowledge concerning these is very imperfect.

§ **405**. *Ferments and other bodies.* Even normal urine has frequently been found to contain a small quantity, hardly amounting to more than a trace, of proteid material, apparently an albumin; but the normal presence of even this small quantity has been disputed. Urine, however, certainly contains ferment bodies.

When urine is treated with many times its volume of alcohol, a granular or flocculent precipitate is thrown down, consisting chiefly of phosphates, together with some other substance or probably several other substances, in very small quantities. An aqueous solution of the precipitate, which may be freed from the phosphates, is both amylŏlytic and proteolytic. Ferments may also and more readily be extracted from urine by allowing shreds of fibrin to soak in the urine for a few hours, and then removing and washing them. The ferments become entangled in the fibrin in such a way as not to be easily removed by washing. The washed shreds will convert starch into sugar; and when treated with dilute hydrochloric acid digest themselves, shewing the presence of pepsin. By this method it has been ascertained that an amylolytic ferment and pepsin are present in quantities which vary in the twenty-four hours according to the meals. Rennin has also been found, and at times at least, trypsin. From this it appears that some of the ferments of the alimentary canal escape from the body by the urine, being probably re-absorbed directly from the respective glands; the quantity moreover which thus escapes is insignificant.

A small quantity of gas, about 15 vols. p.c., can be extracted by the mercurial pump from urine received direct from the body without exposure to air. The gas so obtained consists chiefly of carbonic acid, nitrogen being very scanty, and oxygen occurring in very small quantities or being wholly absent. The meaning of this we have already touched upon in speaking of respiration, see § 359.

§ **406**. The quantities in which these multifarious bodies, all of which as we have seen we may perhaps regard as constituents of normal urine, are present in different specimens of urine, vary within very wide limits, being dependent on the nature of the food taken, and on the conditions of the body. The amount not of water only, but of many of the other several constituents, varies widely and indeed rapidly, so that the percentage composition of urine will vary from hour to hour if not from minute to minute. The causes which determine these variations in the nature and amount of urine we shall study later on. Meanwhile what may be called the average composition of human urine is shewn in the following table in which the acids and bases are put down separately.

AMOUNTS OF THE SEVERAL URINARY CONSTITUENTS PASSED IN TWENTY-FOUR HOURS. (After Parkes.)

	By an average man of 66 kilos.		Per 1 kilo of body weight.
Water		1500·000 grammes	23·0000 grammes
Total Solids			1·1000
Urea	33·180		·5000
Uric Acid	·555		·0084
Hippuric Acid	·400		·0060
Kreatinin	·910		·0140
Pigment, and other substances	10·000		·1510
Sulphuric Acid	2·012		·0305
Phosphoric Acid	3·164		·0480
Chlorine	7·000		·1260
	(8·21)		
Ammonia	·770		
Potassium	2·500		
Sodium	11·090		
Calcium	·260		
Magnesium	·207		
		72·000	

§ **407**. *The Acidity of Urine.* The healthy urine of man is acid, owing to the presence of acid sodium phosphate, the absence of free acid being shewn by the fact that sodium hyposulphite gives no precipitate. The amount of acidity is about equivalent to 2 grms. of oxalic acid in twenty-four hours, but the degree of acidity at any one time varies much during the day, being in an inverse ratio to the amount of acid secreted by the stomach; thus it decreases after food is taken, and increases again as gastric digestion comes to an end. It varies with the nature of the food; with a vegetable diet the excess of alkalis in the food, being secreted by the urine, leads to alkalinity, or at least to diminished acidity, whereas this effect is wanting with an animal diet, in which the alkalis are less abundant, earthy bases preponderating. Hence the urine of carnivora is generally very acid, while that of herbivora is alkaline. The latter, when fasting, are for the time being carnivorous, living entirely on their own bodies, and hence their urine becomes under these circumstances acid.

The natural acidity increases for some time after the urine has been discharged, owing to the formation of fresh acid, apparently by some kind of fermentation. This increase of acid frequently causes a precipitation of urates, which the previous acidity, even after the cooling of the urine, had been insufficient to throw down. After a while however the acid reaction gives way to alkalinity. This is caused by a conversion of the urea into ammonium carbonate through the agency of a specific 'organized' ferment. This ferment as a general rule does not make its appearance except in urine exposed to the air; it is only in unhealthy conditions that the fermentation takes place within the bladder, and in such cases is due either to micro-organisms introduced into the bladder from without, during the use of instruments for instance, or to the action of an unorganized ferment, secreted apparently by the walls of the bladder.

§ **408**. *Abnormal Constituents of Urine.* The structural elements found in the urine under various circumstances are blood, pus and mucus corpuscles, epithelium from the bladder and kidney, and spermatozoa. To these may be added the so-called 'casts' which are either 'epithelial casts,' that is to say cylinders of more or less altered epithelial cells shed from the tubules, or structureless 'fibrinous' casts, which are cylinders of peculiar material moulded in the lumina of the tubules; the exact nature of this material is at present a matter of doubt; it is not always the same but appears not to be fibrin.

The most common and important abnormal constituents of urine are *albumin*, giving rise to albuminuria, and *sugar*, giving rise to glycosuria or diabetes. The soluble proteids generally spoken of as 'albumin' in the urine differ in different cases. The exact determination of their nature is a matter of some difficulty, since, as we have seen, we have in differentiating the various proteids to trust largely to their behaviour as regards precipitation upon the addition of certain saline bodies; and the presence of saline bodies in the natural urine introduces complications. It would appear, however, that the proteids usually present are serum-albumin and globulin; these are not however as a rule, if ever, present in the same relative proportions as in blood-plasma; and either the one or the other may be present by itself. A form of albumose (§ 203) called *hemi-albumose*, is sometimes found, and indeed probably very many distinct kinds of proteids are from time to time present. If egg-albumin be injected into the blood it appears in the urine as egg-albumin, and peptone similarly injected appears as peptone.

The sugar which is found in the urine of diabetes is undistinguishable from ordinary dextrose; but whether it is absolutely identical with that body, or whether the sugar in all cases of diabetic urine is exactly the same, cannot perhaps as yet be regarded as definitely settled.

When blood is mingled with urine in the kidney and in the urinary passages the constituents of the former are of course added to those of the latter; and when as sometimes happens chyle from the lacteals makes its way into the kidneys the urine contains the fats and other constituents of chyle. Fats, however, may be present without the urine being distinctly 'chylous.'

Cholesterin, bile-acids, bile-pigments, and one or other of a large number of bodies arising from a disordered metabolism of the body, such as leucin, tyrosin, acetone (in cases of diabetes), oxalic acid, taurin, cystin and many others are also found more or less frequently; some of these indeed have been regarded as normal constituents. Besides these the urine serves as the chief channel of elimination for various bodies, not proper constituents of food, which may happen to have been taken into the system. Thus various minerals, alkaloids, salts, pigmentary and odoriferous matters, may be passed unchanged. Many substances thus occasionally taken undergo, however, changes in passing through the body; the most important of these, since the changes which they undergo throw light on the metabolic processes of the body, will be considered in a succeeding chapter.

SEC. 3. THE SECRETION OF URINE.

§ 409. The facts which we have learnt in a preceding section concerning the structure of the kidney have shewn us that that organ, unlike the other secreting organs which we have hitherto studied, consists of two parts, so distinct in structure that it seems impossible to resist the conclusion that their functions are different, and that the mechanism by which the urine is secreted is of a double kind. On the one hand the tubuli uriniferi with their characteristic epithelium seem obviously to be actively secreting structures comparable to the secreting alveoli of the salivary and other glands. On the other hand the Malpighian capsules with their glomeruli are organs of a peculiar nature with an almost insignificant epithelium, and their structure irresistibly suggests that they act rather as what may be called in a general way a filtering than as a truly secreting mechanism. Hence has arisen the view, which frequently bears the name of Bowman since he was the first to put it forward, that certain constituents only of the urine are secreted after the fashion of other secreting glands by the tubuli uriniferi, and that the rest of the constituents, including a great deal of the water with such highly soluble and diffusible salts as preexist in adequate quantity in the blood, are as it were filtered off by the glomeruli of the Malpighian capsules. We shall see later on reason to doubt whether we are justified in applying the term 'filtration,' which has a definite physical meaning, to the process by which water and other substances pass from the blood vessels of the glomerulus into the lumen of the tubule; for that process is as we shall find peculiar and complex. But such a doubt need not prevent us from recognizing that the whole act of secretion of urine consists of two parts, one of which is much more closely dependent on the flow of blood through the kidney than is the ordinary process of secretion such as has hitherto come before us, and another part which seems to bear the same relation to the flow of blood as does ordinary secretion.

That the work of the kidney is to an unusual degree dependent on the flow of blood through it seems suggested by the vascular arrangements; for these are extremely favourable to a full and rapid stream of blood through the organ. The short and relatively broad renal artery comes off direct from the abdominal aorta, where the blood-pressure is extremely high; the renal vein opens directly into the vena cava, where the blood-pressure is extremely low. Between the mouth of the renal artery and the mouth of the renal vein the difference of pressure is very great indeed; and as we have seen in treating of the vascular system it is the difference of pressure between two points of the vascular tract which is the actual cause of the flow of blood from the one point to the other. The difference of pressure indeed which drives the blood through the limited area of the kidney is the same difference of pressure which drives the blood along the abdominal aorta down both legs back again to the vena cava.

This free and abundant supply of blood is regulated, is either increased or diminished, according to the needs of the moment, by the vaso-motor system; this is shewn by experimental and other results, which it will be profitable to study in some detail. Before entering into these details, however, it will be well to call attention to the fact that when vaso-motor events modify the flow of blood through an organ they produce their effects in one direction or another by working on arterial blood-pressure. Thus, as we shall see, when stimulation or section of a nerve increases the flow of blood through the kidney it does so by increasing the pressure in the small vessels of the kidney, including the capillary loops of the glomeruli. In such a case the walls of the glomerular loops, through which the passage of materials to form (part of) the urine takes place, are subjected to two influences; on the one hand to a fuller, more rapid flow of blood past them, and on the other to an increase of the pressure which that blood as it passes along exerts on them. We shall have subsequently to discuss the share taken by these two influences in determining and modifying the passage of material through the walls of the glomerular loops; and this will bear on the question of filtration to which we have above alluded; but for the present it will be convenient to deal with the effects of variation in blood-pressure apart from this secondary question.

§ **410**. *The vaso-motor mechanisms of the kidney.* It may be shewn experimentally that the kidney is supplied with a vaso-motor mechanism as well-developed perhaps as that of any other part of the body. By means of a modification of the plethysmograph (Figs. 88, 89), we can readily observe the variations which take place in the volume of the kidney.

The instrument consists of two parts, one of which (Fig. 88), called the oncometer[1], is applied to the organ about to be studied, while the other (Fig. 89), called the oncograph, is the recording part of the apparatus. Any diminution in the volume of the organ (Fig. 88, *K*), kidney, spleen, &c. as the case may be, diminishes the pressure on the fluid in the chamber *a*; some of the fluid in the chamber *M* (Fig. 89) accordingly passes through the tube *K* (Fig. 89) and the tube *T* (Fig. 88) to the chamber *a*; the piston *D* accordingly falls and with it the lever *H*. Similarly an increase in the volume of the organ causes the lever to rise.

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[1] From *oncos*, bulk.

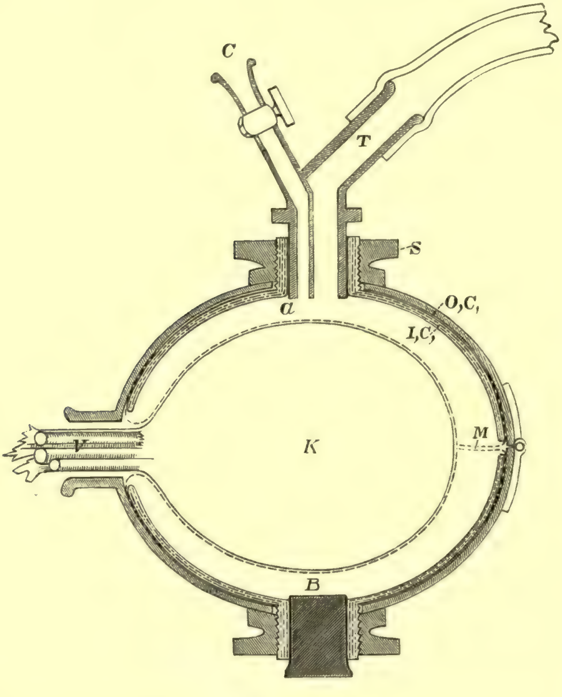

Fig. 88. Renal Oncometer. Seen in section (semi-diagrammatic). *K.* kidney, *V.* vessels and nerves imbedded in fat, &c. entering hilus of organ, *O.C.* and *I.C.* outer and inner metal capsules screwed together by the screw *S*, and holding between them the edge of the membrane *M* which applies itself to the surface of the kidney, and forms with the metal capsule two chambers *a* and *B*, one of which (*B*) is closed by a plug filling the opening *B*, while the other (*a*) communicates by a tube *T* with the recording instrument. The other opening *C* (which is closed by a small tap) is for the purpose of filling the chamber *a* with warm oil, after the kidney has been placed in the box, the other chamber *B* having been previously partly filled, the quantity introduced into it depending upon the size of the kidney.

The volume of the kidney may be increased by a swelling of its constituent cells and other structural elements, by an accumulation of lymph in its lymph-spaces, and by a distension of its blood vessels. Compared with the third, the two former causes are in health so insignificant and problematical that they may be disregarded. Further, the distension of the blood vessels will in general depend on the constriction or dilation of the renal arteries

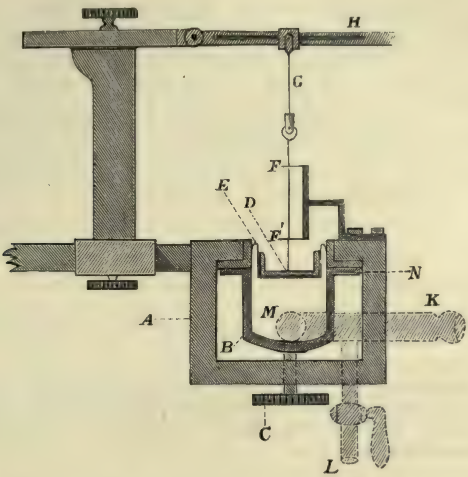

Fig. 89. Semi-diagrammatic sectional view of Oncograph. Half natural size. *K* tube connecting instrument with oncometer. *D* piston floating on oil contained in the cavity *M*; the oil is prevented from escaping by the side of the piston by the delicate flexible membrane *E*, which does not interfere with the movements of the piston. *H*, recording lever connected with the piston by a needle *G* passing through the guides *F*, *F′*. The screw *C* is for the purpose of clamping the edge of the membrane between the two ring-shaped surfaces at *N*, while the side tube *L* is for the purpose of filling the instrument.

and their ramifications, for distension due to venous obstruction will only occur in special cases. Hence variations in the volume of the kidney may be taken as a measure of variations in its vascular supply, increase of volume indicating dilated renal vessels, and decrease of volume indicating constriction of the renal vessels.

When by means of the instrument just described a tracing is taken of the volume of a kidney in what may be considered a normal condition, some such result as that shewn in Fig. 90 is obtained.

The volume of the kidney is seen to be so delicately responsive to changes in the mean arterial pressure that the curve reproduces almost exactly a blood-pressure curve, shewing not only the respiratory undulations, but even the rise and fall due to the individual heart-beats. With each rise of mean arterial pressure more blood is driven into the renal vessels and the kidney swells: with each fall of pressure less blood enters and the kidney shrinks. On other tracings taken in the same way may often be seen (not shewn in Fig. 90) the wider variations corresponding to the

Traube-Hering curves; but it will be observed that in these the kidney shrinks with the rise of pressure and swells with the fall.

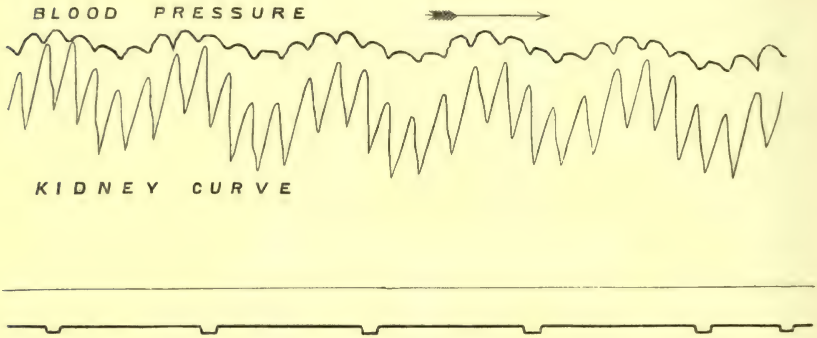

Fig. 90. Blood-pressure tracing, and Curve from Renal Oncometer. Natural size. The blood-pressure abscissa line has been raised 2·75 cm. (the actual medium blood-pressure having been 115 mm. Hg.). The time-curve gives interruptions recurring every three seconds.

For as we have seen (§ 388) the rise in the Traube-Hering undulation is due to an augmentation of peripheral resistance caused by the constriction of minute arteries; and this constriction occurs in the kidney as elsewhere; the renal arterioles take their share in producing the result, and in consequence of their constriction the kidney shrinks. Similarly the relaxation of the renal vessels contributes to bring about the sequent fall.

§ **411**. In the course of a discussion in an earlier part of this work (§ 171) on the local and general effects of arterial constriction and dilation, we saw that the local blood-pressure in and flow of blood through the capillaries and other minute vessels of this or that vascular area may be *increased*—

1. By an increase of the general blood-pressure, brought about—(*a*) by an increased force, frequency, &c. of the heart's beat, (*b*) by the constriction of the small arteries supplying areas other than the area in question.

2. By a relaxation of the artery (or arteries) supplying the area itself, which, while diminishing the pressure in the artery itself, increases the pressure in the capillaries and small veins which the artery supplies. It need hardly be added that this local relaxation must not be accompanied by a too great dilation elsewhere.

The same local blood-pressure and flow of blood may similarly be *diminished*—

1. By a constriction of the artery of the area itself (and its branches), which, while increasing the pressure on the cardiac side of the artery, diminishes the pressure in the capillaries and veins

which are supplied by the artery. This again must not be accompanied by a too great constriction elsewhere.

2. By a lowering of the *general* blood-pressure, brought about —(*a*) by diminished force, &c. of the heart's beat, (*b*) by a general dilation of the small arteries of the body at large, or by a dilation of vascular areas other than the area in question.

Applying these considerations to the blood vessels of the kidney, we should expect to find the following.

A rise in general blood-pressure, and that means a rise of pressure in the abdominal aorta at the mouth of the renal artery, will cause a greater flow of blood through, and so an expansion of the kidney, provided that the renal arteries themselves are not unduly constricted at the same time. This is well shewn, as we have seen, in the curve given above, where the increase of pressure due to each heart beat, as well as that due to each respiratory movement, being of central origin and not due to arterial constriction and being unaccompanied by any compensating constriction of the renal artery, leads to expansion of the kidney, that is, to a greater flow of blood through the kidney.

If, however, the rise of general blood-pressure be due to events which at the same time cause a constriction of the renal arteries, the flow through the kidney may not only not be increased but even be diminished; the kidney may shrink instead of expanding. Thus if dyspnœa be brought about, as by stopping artificial respiration during an experiment, the kidney at once shrinks; the too venous blood stimulates the vaso-motor centre, and probably also by direct action on the blood vessels leads to a general arterial constriction and so to a rise of blood-pressure; but the renal vessels are involved in this constriction, so much so that their constricted condition more than counterbalances the general rise of blood-pressure, and less blood flows through the renal vessels. So also when the medulla or spinal cord is directly stimulated by induction shocks (the animal being under urari so as to eliminate the complications due to contractions of the skeletal muscles) the renal vessels share so fully in the arterial constriction which results that, in spite of the great rise of mean pressure which is induced, less blood than normal passes through the renal vessels, and the kidney shrinks. Or if the abdominal splanchnic nerves be stimulated, since as we shall see these carry vaso-constrictor fibres for the kidney, in spite of the rise of blood-pressure which follows, the kidney shrinks on account of the great constriction of the renal vessels.

On the other hand if a rise of blood-pressure be for any reason not accompanied by a compensating constriction of the renal arteries, that rise, whether it be brought about by general constriction of arteries other than the renal or by an increase of the cardiac delivery, causes the kidney to swell, shewing a greater flow of blood. Such a condition of things may be induced by section of the nerves of the renal plexus, whereby the paths of all vaso-constrictor impulses to the kidney are blocked. After this has been done a rise of general pressure whether by dyspnœa, or by direct stimulation of the spinal cord, or by stimulation of the abdominal splanchnic nerves, leads to a greater flow through the renal vessels and an increased expansion of the kidney.

A rise of general blood-pressure then may be accompanied by either a shrinking or a swelling of the kidney, by either a greater or a less flow of blood through the kidney, according to the concomitant condition of the renal vessels; or indeed may under certain circumstances be accompanied by no change at all in the renal circulation, the local effects exactly counterbalancing the general ones.

Conversely, in a similar way, a fall of blood-pressure leads to a lesser flow through the renal vessels and a shrinking of the kidney unless it be accompanied by a dilation of the renal vessels out of proportion to the general fall. Thus when the spinal cord is divided below the medulla the fall of general blood-pressure is, as we have seen (§ 173) very marked, being due to an abolition for the time being of wonted constrictor impulses. The pressure in the aorta falls rapidly, and at the same time, owing to the more open pathway through the region of peripheral resistance in the body generally, the pressure in the vena cava is increased; the difference of pressure between the mouth of the renal artery in the aorta and the mouth of the renal vein in the vena cava is so largely reduced that in spite of the concomitant relaxed condition of the renal vessels themselves the flow of blood through the kidney is largely diminished.

It will of course be understood that, the general blood-pressure remaining the same, the flow through the kidney will at once be on the one hand increased by dilation and on the other decreased by constriction of the renal vessels themselves. The constricted or dilated condition of the renal vessels can by themselves produce but little effect on the pressure either in the aorta or in the vena cava; and the difference between the pressure at the mouth of the renal artery and that at the mouth of the renal vein remaining the same, the more open passages of the dilated renal vessels must lead to a fuller, and the narrower passages of the constricted renal vessels to a scantier flow, through the kidney.

§ **412**. By means of the oncometer, watching the shrinking and swelling of the kidney and thus judging of the flow of blood through it, the results being always interpreted with reference to the general blood-pressure on the lines of the above discussion, the paths of vaso-motor impulses to the kidney have been approximately made out. Vaso-constrictor fibres for the kidney are supplied from what we have previously (§ 169 and elsewhere) spoken of as the vaso-constrictor region of the spinal cord. They issue from the spinal cord by the anterior roots of a large number of the spinal nerves taking origin from this region, and may be traced (in the dog) as high up as the 6th dorsal, a few perhaps even to the 4th dorsal, and as low down as the 2nd lumbar (4th lumbar if only 13 nerves be counted as dorsal); but most seem to pass by the 11th, 12th and 13th dorsal nerves. Passing through the corresponding ganglia of the splanchnic (sympathetic) chain, these fibres reach the solar plexus and thus the renal plexus by the abdominal splanchnic nerve; those however coming from some of the lower nerves apparently do not contribute to the splanchnic nerve, but take a separate course. Centrifugal stimulation of these anterior roots produces shrinking of the kidney, all the more marked and distinct in the case of the 11th, 12th and 13th dorsal roots because the effect on the kidney is then not so much masked by vaso-motor effects on other organs. Stimulation of the higher roots also produces shrinking of the kidney but less marked, since in these cases the stimulation bears at the same time largely on vaso-constrictor fibres for other abdominal organs, and so by raising the general blood-pressure tends to neutralize the local effect on the kidney. And even the very decided shrinking of the kidney which results from the stimulation of the splanchnic trunk itself is less than would take place if the stimulation affected the vessels of the kidney only.

§ **413**. We stated in § 168 that by the method of slowly repeated rhythmical stimulation the presence of vaso-dilator fibres in the sciatic nerve might be detected, though these are largely mixed with vaso-constrictor fibres; and slow rhythmical stimulation of the anterior roots of the above-mentioned lower dorsal nerves leads, not, as does ordinary rapidly interrupted stimulation, to shrinking, but to swelling of the kidney, shewing that these roots contain vaso-dilator fibres as well as vaso-constrictor fibres. The higher (anterior) roots also appear to contain some renal vaso-dilator fibres; but the effect of stimulating them by the slow rhythmic method is more masked by a concomitant dilation of the vessels of the other abdominal organs, the roots in question containing vaso-dilator as well as vaso-constrictor fibres for those organs; this leads to a fall of general blood-pressure whereby the tendency of the kidney to swell is counteracted. As far as can be ascertained at present the paths of the renal vaso-dilator fibres are similar to those of the renal vaso-constrictor fibres.

The kidney then is well supplied, especially through the anterior roots of the 11th, 12th and 13th dorsal nerves, with vaso-constrictor fibres, and is also supplied with vaso-dilator fibres. Some results have seemed to shew that the fibres passing along the roots of one side of the spinal cord govern the vessels not only of the kidney of the same side but also to a certain extent of the kidney of the other side; it seems doubtful, however, whether this is really the case.

There is no satisfactory evidence that the vagus nerve of either side contains any vaso-motor fibres reaching the kidney (see § 399).

§ **414**. It is obvious then that by means of this vaso-motor mechanism the flow of blood through the kidney is governed by the central nervous system in such a way that afferent impulses, started in this or that region or surface, and passing up to the central nervous system, may lead either to constriction or to dilation of the renal vessels; and to such actions of this kind we shall presently return. Meanwhile, we wish to call attention to the fact that the volume of the kidney is remarkably sensitive to chemical changes taking place in the blood. The injection into the blood of even a small quantity of water causes a transient shrinking of the kidney followed by a more lasting expansion. The injection of urea and some other diuretics produces the same effect to a more marked degree, leading especially to a swelling which lasts for some considerable time, while the injection of normal saline solution, and especially of such diuretics as sodium acetate, causes an expansion from the very first, the primary shrinking being absent. It is moreover worthy of note that these effects of diuretics and of chemical changes in the blood are observed even after all the renal nerves have apparently been completely severed. Hence the changes in volume caused by the presence of these substances in the blood must be due to the substances acting either upon some peripheral vaso-motor mechanism, or, even more directly, on the blood vessels themselves. It may be added that they will produce considerable effects in the kidney itself without appreciably modifying the general blood-pressure.

§ **415**. If, while the kidney is in the oncometer, and the various experiments on section and stimulation of nerves and the like are being carried on, a cannula be tied in the ureter, the secretion of urine may be watched at the same time. It will then be seen that the flow of urine through the end of the cannula is not equable, and does not either increase or decrease in an even manner. On the contrary, it will frequently be found that a sort of gush of urine takes place, several drops following each other in rapid succession, followed by a cessation of flow; and if the ureter be watched it will be seen that the gushes of urine are synchronous with waves of peristaltic contraction sweeping down the ureter. Obviously the urine collects to a certain extent in the pelvis of the kidney and is driven thence by muscular action from time to time; to this point we shall return later on.

Making every allowance, however, for these irregularities of flow, we may take the rate of flow from the end of the cannula as a measure of the rate of secretion; and it is found that as a general rule increased flow of urine is coincident with swelling of the kidney, that is with a greater flow of blood through it, and diminished or arrested flow of urine is coincident with shrinking of the kidney, that is with a diminished flow of blood through it.

A striking instance of this is afforded by the experiment of dividing in the dog the spinal cord below the medulla. The blood-pressure then, as we know, falls rapidly, owing to the removal of constrictor impulses from the small arteries and the great diminution of peripheral resistance which follows upon so many small arteries becoming dilated; and though the renal arteries probably share in the general relaxation yet, owing to the fall of pressure in the aorta conjoined as this is by a corresponding rise of pressure in the vena cava, the flow of blood through the kidney is largely diminished. We find that after the operation the secretion of urine is greatly diminished; indeed, in most cases, the flow from the end of a cannula is almost arrested. In fact we may almost make the general assertion that, when in the dog the blood-pressure falls to about 30 mm. Hg or less, the secretion of urine is for the time stopped. These and other results support the view stated above that the secretion of urine is in quite a special way dependent on the flow of blood through the kidney; and we may further conclude that the secretion which is so particularly influenced by the flow of blood is that special kind of secretion, allied to filtration, which takes place through the glomeruli, and not the more ordinary kind of secretion by means of the epithelium of the tubuli uriniferi. But before we proceed to discuss how the increased flow of blood increases the glomerular flow of urine, we must turn to consider the functions of the epithelium of the tubuli.

Secretion by the Renal Epithelium.

§ **416**. The glomerular mechanism is after all a small portion only of the whole kidney, and the epithelium over a large part of the course of the *tubuli uriniferi* bears most distinctly the characters of an active secreting epithelium. These facts would lead us *à priori* to suppose that the flow of urine is in part the result of an active secretion comparable to that of the salivary or other glands which we have already studied. And we have experimental and other evidence that such is the case.

In the first place a flow of urine may be artificially excited even when the natural flow has been arrested by diminution of blood-pressure. Thus if, when the urine has ceased to flow in consequence of a section of the medulla oblongata, certain substances, such as urea, urates, sodium acetate, and the like, be injected into the blood, a more or less copious secretion is at once set up. This secretion is, or at least may be, unaccompanied by any rise of general blood-pressure sufficient to account for the increased secretion as the mere result of an increased flow of blood. It is true (as we have seen § 414) that the injection of these substances leads to an expansion of the kidney, an expansion which is probably due to a local dilation of the small renal arteries; but the flow of urine which is observed in these cases is too great to be accounted for by any increase of flow of blood which the local dilation may bring about; and hence we conclude that the increase of secretion is of a different kind from that which follows upon mere increase of blood-flow. It seems much more reasonable to suppose that the presence of the above substances in the blood excites the renal epithelium cells to an unwonted activity, causing them to pour into the interior of the tubules a copious secretion, just as the presence of pilocarpin in the blood will cause the salivary cells to pour forth their secretion into the lumen of their ducts; and that this activity of the epithelium cells is accompanied, also as in the case of the submaxillary and other glands, by a vascular dilation, which, though adjuvant and beneficial, is not the distinct cause of the activity. This view is further supported by the following remarkable experiment, which goes far to shew that of the various substances which having found their way into the blood are thrown out by the kidney, some pass into the urine through the glomeruli while others are distinctly secreted by the tubuli uriniferi, the discharge of the latter being accompanied by a general activity of the secreting cells, as shewn by the flow of water taking place at the same time.

In the amphibia, the kidney has a double vascular supply: it receives arterial blood from the renal artery, but there is also poured into it venous blood from another source. The femoral vein divides at the top of the thigh into two branches, one of which runs along the front of the abdomen to meet its fellow in the middle line and form the anterior abdominal vein, while the other passes to the outer border of the kidney and branches in the substance of that organ, forming the so-called renal portal system. Now the glomeruli, in some species at least of these animals, are supplied exclusively by the branches of the renal artery, the renal vena portæ only serving to form the capillary plexus around the tubuli uriniferi, which is also supplied by the efferent vessels of the glomeruli. From this it is obvious that if the renal artery be tied, the blood is shut off entirely from the glomeruli; and actual observation of the kidney has, in the animals in question, shewn that under these circumstances there is no reflux from the capillary network surrounding the tubules back to the glomeruli; thus the kidney by this simple operation is transformed into an ordinary secreting gland devoid of any special filtering mechanism. Such a kidney may be used to ascertain what substances are excreted by the glomeruli, and what by the tubules in some other part of their course. It is found that urea injected into the blood gives rise to a secretion of urine when the renal arteries are tied; this substance therefore is secreted by the epithelium of the tubules, and in being so secreted gives rise at the same time to a flow of water through the cells into the interior of the tubules. Sugar and peptones, on the other hand, which injected into the blood readily pass through the untouched kidney and appear in the urine, do not pass through a kidney the renal arteries of which have been tied, even when a diuretic such as urea is given at the same time in order to secure a flow of urine. These substances therefore are excreted by the glomeruli.

The validity of this experiment, which may be accepted as indicating a marked difference between glomerular secretion on the one hand and epithelial or tubular secretion on the other, depends on the absence of any collateral circulation whereby the glomeruli may be supplied with blood after ligature of the renal artery. In these animals anatomoses occur between the renal arteries and the arteries of the generative organs; and unless the renal artery be so tied as to avoid these collateral communications the results of the experiment are different.

Additional evidence in favour of the secretory activity of the epithelium cells is afforded by the following observation. Into the veins of animals in which the urinary flow had been arrested by section of the spinal cord below the medulla a quantity of the blue colouring material known as sodium sulphindigotate[1] is injected. This substance is rapidly excreted on the one hand by the liver in the bile, and on the other hand by the kidney. By varying the quantity injected, killing the animals at appropriate times after the injection of the material, and examining the kidneys microscopically and otherwise, it may be ascertained that the pigment so injected passes from the blood into the renal epithelium, and from thence into the channels of the tubules. There being no stream of fluid through the tubules, owing to the arrest of urinary flow by means of the preliminary operation, the pigment travels very little way down the interior of the tubules, and remains very much where it was cast out by the epithelium cells. There are no traces whatever of the pigment having passed by the glomeruli; and the cells which appear most distinctly to take up and eject it, are those lining such portions of the tubules (viz. the first and second convoluted tubules, zigzag tubules and ascending limbs of the loops of Henle) as from their microscopic features have been supposed to be the actively secreting portions of the entire tubules. The following observation which has been made is of a peculiarly interesting character. After injecting a certain quantity of pigment, and allowing such a time to elapse as might be judged from previous experiments would suffice for the passage of the material through the epithelium to be pretty well completed, a second quantity was injected. It was found that the excretion of this second quantity was most incomplete and imperfect. It seemed as if the cells were exhausted by their previous efforts, just as a muscle which has been severely tetanized will not respond to a renewed stimulation.

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[1] Sometimes called indigo-carmine, though this name is more properly applied to a crude impure preparation of potassium sulphindigotate.

The above observation may be objected to on the ground that this colouring matter does not occur as a constituent of the blood either in health or disease, and especially that the absence of any concomitant discharge of fluid from the cells excites suspicion that the process observed was not really one of secretion; for the injection of such substances as urea or urates into the blood does cause a copious flow of fluid, and indeed thus prevents the microscopic tracking out of their passage, which in the case of urates might otherwise be done much in the same way as with the sodium sulphindigotate. Moreover other observers have maintained that the sodium sulphindigotate does like ordinary carmine pass through the glomeruli. But their results may probably be explained by the glomeruli having been damaged by a too rapid or too abundant injection; and in the case of the amphibian kidney, when sodium sulphindigotate is injected after ligature of renal arteries, no urine is found in the bladder, but the pigment can be traced through the epithelium of the secreting portions of the tubules. Without insisting too much on the value of the sodium sulphindigotate experiments, they may be taken as fairly supporting the view which we are considering. We may add that in birds, the urine of which contains little water, urates may be detected in the epithelium of the tubules but not in the capsules.

Though much remains to be cleared up, we may, for the present, conclude that the secretion of urine does consist of two separate and distinct acts: secretion by the glomeruli, which we may for brevity's sake speak of as glomerular secretion, and secretion by the epithelium of the tubuli, which we may speak of similarly as tubular secretion. Both these forms of secretion, especially the former but to a certain extent the latter also, differ from the secretion of such a gland as the salivary, and both deserve some special consideration.

§ **417**. *The nature of glomerular secretion.* We have seen that the expansion of the kidney which has for its accompaniment an increased flow of urine is one brought about by the renal artery and its various branches becoming dilated, under such circumstances that the difference between the blood-pressure in the aorta at the mouth of the renal artery and the blood-pressure at the vena cava at the mouth of the renal vein is at the same time increased, or at all events is not diminished. We say the renal artery and its various branches since our present knowledge will not enable us to make a more exact statement. It is of course possible that nervous impulses passing along particular nerve fibres should confine their efforts to relaxing the coats of the vasa afferentia of the glomeruli and not pass to the other branches of the renal artery, in which case the circulation of the glomeruli would be exclusively (or nearly so) affected; but of this at present we know nothing, and the general argument remains good if we speak simply of the branches of the renal artery as a whole.

In dealing with the vascular system we saw that relaxation of a small artery, taking place without any marked change in the general blood-pressure and in neighbouring arteries, leads to a fuller and more rapid stream of blood through the capillaries supplied by the artery, and that at the same time the pressure in the capillaries themselves is increased; owing to the decrease of peripheral resistance through the widening of the artery, the great fall of pressure (see § 116) so characteristic of the peripheral region is shifted from the arterial side of the capillaries towards the venous side and to the capillaries themselves.

Hence, as we have already said, when the renal artery dilates two things happen in the loops of the glomeruli: a fuller, more rapid stream of blood passes through them, and that blood as it flows through them is exerting a greater pressure than before on their walls. How does each of the events stand towards the secretion of urine?

We have not at present the means of inducing a fuller and more rapid flow without increasing the pressure; but we may easily obtain increase of pressure without the fuller and more rapid flow. If we hinder or obstruct the outflow through the renal vein we at once increase the pressure in the glomerular loops as in the other capillaries of the kidney. Now, when the blood-pressure in the glomeruli is thus raised by partial obstruction to the venous outflow, the flow of urine so far from being increased is diminished. Obviously then the passage of water and material through the walls of the glomerular loops, to go to form the urine, is not the result of mere pressure, and cannot therefore be spoken of properly as a process of filtration. (Cf. § 302.) And we may here draw a comparison between the passage of water and material through the wall of a capillary in an ordinary situation to form lymph and the passage through the wall of the glomerular loop to form urine or part of urine. The former as we have seen (§ 302) appears to be directly dependent on pressure, though influenced as we have also seen in a very material way by the condition of the vascular wall; and hindrance to venous outflow, so inefficient in promoting a flow of urine, is as we have seen especially favourable to the transudation of lymph. In the former case the substances which pass through the capillary wall may be described as the constituents of the blood generally, proteids as well as salts and other soluble and diffusible matters. Through the wall of the glomerular loop there pass, so long as that wall is sound and intact, neither albumin nor globulin nor fibrin factor, but only water accompanied by some, and apparently a selection of some, of the soluble diffusible constituents of the blood; for, as we have said, the presence of proteids in normal urine is contested, and, at most, there is present a very small quantity only (which moreover may come from the tubular epithelium). This difference in the material which passes through may be referred to the differences in the nature of the partition. The transudation of lymph takes place through the capillary wall; between the blood on one side and the lymph in the lymph-space on the other is only the thin film of conjoined epithelioid plates. But the corresponding wall of the glomerular loop is covered over and wrapped round so to speak by an adherent layer of cells, which though reduced and thin are still epithelial cells; the materials which go to form urine have to pass through these cells as well as through the film of epithelioid plates. It seems to be this layer of cells which determines what shall pass and what shall not.

Obviously the passage through this epithelium is of a peculiar nature. The necessary condition for the due accomplishment of the passage is as we have seen a full and rapid stream of (arterial) blood; the high pressure which accompanies that full and rapid stream, though probably under normal circumstances an adjuvant, is by itself helpless. Thus when the pressure is raised by venous obstruction, in which case the high pressure is accompanied by a slow stream or by actual arrest of the flow, even the passage of mere water is retarded. Seeing that many of the constituents of urine are diffusible substances certainly preexisting in the blood, inorganic salines for instance, and seeing that, if we may trust the experiments on the amphibian kidney spoken of above, diffusible abnormal constituents of blood, such as peptone and sugar, pass into the urine not by the tubular epithelium but by the glomeruli, we might expect that diffusion, in contrast to filtration (see § 312) played an important part in the passage; and a full rapid stream would undoubtedly favour diffusion. But diffusion by itself will not explain matters. Egg-albumin differs very slightly as regards diffusibility from serum-albumin, and yet while at the most a minute quantity only of the latter passes into the urine in normal circumstances, the former when injected into the blood at once makes its way into the urine, presumably by the glomeruli. On the other hand urea is an eminently diffusible body, and yet if we can trust the experiments on the amphibian kidney, the main mass at all events of the urea of the urine passes by the epithelium of the tubules.

The important part played by the epithelium is shewn when the epithelium is deranged. If the renal artery be temporarily ligatured or otherwise obstructed, so that the glomeruli are shut off from their blood-supply for some little time, the secretion of urine is stopped; on reestablishment of the circulation the secretion of urine slowly returns, and the urine is then found to be albuminous, remaining so for some little time. The serum-albumin and globulin which could not pass through the intact epithelium, can pass through when the epithelium is damaged by interference with its nutrition. The appearance of albumin in the urine (albuminuria) is a not infrequent symptom of kidney disease, and its presence in other than minute quantities indicates imperfections in the glomerular epithelium. But even under unhealthy conditions that epithelium still governs to a certain extent the passage of material; for the proteids of the blood-plasma do not pass through bodily or in a proportion which corresponds either to the relative proportion in which they exist in the plasma or to the relative ease (or difficulty) with which they pass through membranes. Though the "albumin" of albuminous urine frequently consists of both serum-albumin and globulin, these do not necessarily occur in the same proportion as in blood; they vary in urine much more than they do in blood; and indeed the one or the other may be absent; moreover fibrin factors are very rarely found.

Hæmoglobinuria, or the presence of hæmoglobin in urine, may be brought about by injecting into the blood vessels laky blood, or some substance such as pyrogallic acid, which will "break up" the corpuscles of the blood. Now in such cases there is evidence that the hæmoglobin passes through the glomeruli; minute disc-like masses of hæmoglobin, the so-called 'menisci,' are, by appropriate methods of preparation, found *in situ* in the capsules. Such a passage is very far removed from being a process of diffusion.

We may conclude then that the passage of material through the glomeruli, like the transudation of lymph and even to a more marked extent, is a complex affair in which the ordinary physical processes of diffusion and filtration may play their part, but are not masters of the situation.

§ **418**. *The work of the epithelium of the tubules.* As we have said the structural features of the epithelium cells of the tubules seem to justify the conclusion that they exercise a secretory activity comparable with that of a salivary or a gastric gland. But their work is in many ways peculiar. In the case of the salivary, gastric, and pancreatic glands there can be no doubt that the specific constituents of the several secretions, mucin, pepsin, trypsin and the like, are manufactured in the alveolar cells out of antecedents of some nature or other. The evidence, as we have seen, is all against the view that these glands merely withdraw, secrete in the old sense of the word, from the blood these substances preexisting in the blood. When the salivary glands are extirpated or the pancreas or the stomach removed there is no accumulation in the blood of the specific constituents of the corresponding secretions. So also when the liver is extirpated there is no accumulation in the blood of either bile acids or bile pigment. With regard to the kidney and the most important constituent of urine, namely urea, the case is different. If the kidneys in a mammal be extirpated, or if the kidneys by disease or by ligature of the ureters be so damaged as to be unable to carry on their work, an accumulation takes place in blood, not as was once thought of some antecedent of urea such as kreatin, but of urea itself. In the case of birds and reptiles which excrete not urea but chiefly uric acid the accumulation is one of uric acid. Obviously in secreting urea the work of the epithelium of the tubules is largely if not exclusively confined to simply picking the urea out of the blood and pushing it so to speak into the lumina of the tubules. We might perhaps say exclusively, for there is no evidence that any urea at all is actually manufactured in the kidney.

But even this mere picking up the urea is after all not a simple process; the epithelial cell of the tubule is not a mere passive sieve of peculiar structure especially adapted to strain off the urea from the blood. As we have already seen, when urea or uric acid is injected into the blood the result is not a mere increase in the proportions of urea (or uric acid) present in the urine which is being secreted. The injection leads to an increased *flow of urine*, the whole activity of the cell is stirred up, and other constituents, not at the moment like the urea existing in excess in the blood, are discharged into the lumina of the tubules together with the urea.

How the urea, which is in this peculiar manner taken out of the blood, comes to make its appearance in the blood is a problem in which the kidney is not concerned and with which we shall deal in treating of the metabolic events of the body generally.

§ **419**. In the case of some other constituents of the urine we have evidence that the cells do something more than simply pick the constituent out of the blood. Hippuric acid, as we have seen, occurs in small quantity in the urine of man, and in larger amount in the urine of herbivora. Now hippuric acid may be formed by the combination, with dehydration, of benzoic acid and glycin ($C_7H_6O_2 + C_2H_5NO_2 - H_2O = C_9H_9NO_3$); and benzoic acid introduced into the alimentary canal or injected into the blood, reappears in large measure in the urine as hippuric acid. Somewhere in the body the benzoic acid meets with and combines with glycin. And we have experimental proof that the combination may and probably does take place in the kidney.

If a circulation of blood be kept up through the blood vessels of the kidney freshly removed from a living animal, and benzoic acid and glycin be added to the blood as it is about to enter into the kidney, hippuric acid will be found in the blood issuing from the kidney, especially if the same blood be passed through the kidney several times; the blood used must be blood containing oxyhæmoglobin, carbonic-oxide-hæmoglobin not producing the effect. The mere mixing with the blood itself is insufficient; and if the blood be sent not through a kidney just removed from the living body but through one taken from a dead body or one which has been left to itself for some time after removal from a living body, the synthesis will not be effected. To carry out the combination by means of the kidney which has been removed from the body the kidney must retain for a while its own life, it must be a "surviving" kidney. Nor is it absolutely necessary to bring the benzoic acid and glycin to the kidney by means of a blood-stream. If a "surviving" kidney be divided rapidly into small pieces and the benzoic acid rapidly mixed with the pieces, hippuric acid is formed. Nor is it necessary to furnish the glycin. If benzoic acid alone be used, hippuric acid is formed all the same. Glycin, as we have previously said, cannot be recognized as a normal constituent of any of the tissues; nevertheless, as we have seen in speaking of glycocholic acid in the bile and as we shall see later on, glycin must make a momentary appearance in various metabolic processes of the body, being immediately on its appearance converted into something else, so that it never remains as glycin. It apparently is formed in the kidney, and is thus momentarily available for the conversion of benzoic into hippuric acid.

It seems probable therefore that, with regard to this particular constituent of urine, hippuric acid, the cells of the tubules have the power of effecting a combination between the benzoic acid brought to them by the blood and the glycin which they furnish by means of their own metabolism, and in this way produce hippuric acid.

Not only benzoic acid but many other bodies taken into the system reappear in the urine combined with glycin, and in their cases also the combination probably takes place through the activity of the cells of the tubules of the kidney. Moreover, other changes than the assumption of glycin, the various changes which many chemical substances taken into the system undergo before reappearing in the urine, probably also take place to a large extent in the kidney, and are also carried out by means of the epithelium of the tubules.

What other constituents of normal urine are produced in this or a similar manner we do not as yet definitely know. The pigment urobilin, which as we have seen is supposed to be a derivative from bilirubin, may be brought ready formed from the liver or may have the finishing touches given to it in the kidney itself; and the other normal or abnormal urinary pigments possibly arise either directly from hæmoglobin or indirectly from that body through the biliary pigment by a transformation taking place in the cells of the tubules. There is also evidence in frogs that acid sodium phosphate is furnished by the cells of the tubules.

In conclusion then we may say that the activity of the epithelium of the kidney appears especially modified, as compared with other secreting glands, to meet the special object which the kidney has to secure. The purpose of the kidney is not to provide a fluid, urine, which can be made use of for the needs of the body, but to cast out waste matters from the body. Hence its secretory activity is limited largely to the mere discharge of matters which reach it preexistent in the blood, though in several cases it gives the final shape to the excreted substance before it passes into the ureter.

§ **420**. We may illustrate the preceding discussions by briefly passing in review some of the more usual ways in which the secretion of urine is in ordinary life modified.

In the preceding section the composition of urine was illustrated by the daily output of the several constituents rather than by a percentage account of any specimen of urine, for the reason that the composition of urine varies within extremely wide limits. This is especially the case as regards the proportion of water to solids. One urine may be of high specific gravity with a small amount of water relatively to the solids, while another may have so little colour and such a low specific gravity as to appear hardly more than water. The reason of these extreme differences lies in the fact that the kidney is not only the channel by which waste solids leave the body but also an important outlet for the discharge of the stream of water which, in order that the various processes of the body may be duly carried on, is continually passing through the system. It is frequently of advantage to the body to discharge through the kidney a large amount of water, more or less irrespective of the solid matters which are so to speak washed away with it; and hence the advantage of the glomerular mechanism so specially adapted for the special discharge of water.

As we shall see presently, to the skin also falls the duty of discharging large quantities of water. The respiratory organs also, as we have seen, serve for the discharge of water; but the amount which the latter put out can only be varied by the inconvenient method of increasing or diminishing the whole act of breathing. Hence we find special relations between the skin and the kidneys correlating the work of the one to that of the other as regards this particular work of the discharge of water.

When the body is exposed to cold the discharge of water from the skin in the form of sweat is checked, and the cutaneous vessels are constricted. At the same time the blood vessels of the abdominal viscera, including the kidneys, are dilated, but not out of proportion to the constriction of the cutaneous vessels, for the general blood-pressure does not fall but if anything rises somewhat. Thus there is established just the state of things which is favourable to a full and rapid stream of blood through the renal glomeruli; and an increased flow of urine results. It is possible, we may perhaps say probable, that the nervous system affords a special tie between the skin and the kidney so that, under the circumstances in question, the renal arteries are dilated even more than those of the other abdominal viscera; but this has not been proved experimentally. It is also possible that by another reflex mechanism of the central nervous system the skin may work upon the kidney not by the vaso-motor nerves alone but also by nerves governing the secretory activity of the tubules; but we have no satisfactory indications of any such mechanisms, and it seems more probable that the connection should be with the glomerular mechanism, since the chief object at all events is to get rid of water.

Conversely, when the body is exposed to warmth the skin perspires freely and the cutaneous vessels are widely dilated; and conversely also the renal and other abdominal vessels are constricted, so that a slow and small stream of blood trickles through the glomeruli, and the urine which is secreted is scanty.

§ **421**. Even more important than its relations to the skin are the relations of the kidney to the water absorbed by the alimentary canal; this is especially seen when large quantities of fluid are drunk. The whole of the water thus introduced into the alimentary canal passes into the blood, for in a healthy organism no amount of fluid drunk, unless it throws the economy out of order, can affect the amount of water present in the fæces. But the addition to the blood of even a very large quantity of fluid does not, as we have seen, by its mere quantity (§ 186), increase the general blood-pressure, and therefore cannot in this way produce what it undoubtedly does produce, an increased flow of urine.

The fluid so absorbed may act on the kidney in two ways. On the one hand as we have seen (§ 414), the injection of water into the blood produces a local dilation of the renal vessels, as indicated by the swelling of the kidney. Thus the absorption of mere water from the alimentary canal may stir up to greater activity the glomerular mechanism, and in so doing may be assisted by the presence of various substances absorbed from the alimentary canal with the water, for some of these also may similarly lead to dilation of the renal vessels.

On the other hand, some or other of the chemical bodies thus passing into the blood with the water drunk may excite the secretory activity of the tubules, and that either by acting directly on the epithelium as they are carried through the kidney in the blood of the renal arteries, or indirectly through some intervention of the central nervous system.

Our knowledge is at present too scanty to enable us to decide which of these two methods is the one usually employed by the organism; but the inordinate flow of urine, so poor in solids as to be little more than water, which may be directed through the kidney by means of an adequate "drinking bout," would lead us to conclude that in such cases the organism, striving, though too often in vain, to free itself from the evils to which it is being subjected, has recourse rather to the simpler glomerular mechanism than to the more expensive tissue-wasting activity of the tubules; and the urine in such cases is probably discharged chiefly by the method of dilating the renal vessels and thus throwing the poisoned blood into the glomeruli.

When however fluid is taken simply as a proper accompaniment of solid food, the increase of urine which results has probably another origin. As we have already said, and as we shall point out more fully later on, the absorption of proteid material, which is a constituent and generally a conspicuous constituent of every meal, leads to a formation of urea; and urea, as we have seen reason to believe, directly stimulates the epithelium of the tubules to secretory activity. And what seems prominently true of urea is probably true of many other products of digestion; so that the increased flow of urine which follows an ordinary meal accompanied with not more than the ordinary amount of fluid, is the result of the labours of the epithelium of the tubules as well as of the fuller stream of blood through the glomeruli.

§ **422**. What has just been said concerning the influence on the kidney of food and water may be applied also to the action of substances which being especially efficacious in promoting a flow of urine when taken into the body are called "diuretics." The several actions of various diuretics are very varied, and it would be out of place to discuss them fully. We may however say that while the action of some appears simple that of others is complex.

Such agents as sodium acetate and potassium nitrate probably produce their effect chiefly by acting directly on the kidney, inducing, as we have seen, § 414, local vascular dilation and so working on the glomeruli, but probably at the same time also stirring up, after the fashion of urea, the epithelium of the tubules to secretory activity, the accompanying fuller stream of blood through the whole kidney being, as in the case of the salivary and other glands, a useful adjuvant.

The diuretic effect of such an agent as digitalis is probably more complex. By increasing the cardiac stroke, and at the same time constricting many small vessels, digitalis raises the general blood-pressure; but the tendency of the increased blood-pressure to increase the flow of urine may be counterbalanced by the constriction of the renal vessels themselves. And while it is a matter of common experience that digitalis is very effective as a diuretic in cardiac disease, there is great doubt whether it really acts as a diuretic in health; in cardiac disease it probably raises the blood-pressure by improving the cardiac stroke and not by constriction of the blood vessels. But even in the absence of cardiac disease, digitalis has been found in certain cases to act as a powerful diuretic, and in these cases either it must act directly on the tubular epithelium or its effects in constricting the renal arteries must be less than its effects on other small arteries or must pass off before the influence of the heightened blood-pressure has disappeared.

§ **423**. Quite removed from the intervention of chemical substances in the blood and yet most striking is the influence on the kidney of the central nervous system. The potent influence of emotions in promoting the secretion of urine is proverbial, and the general features of 'nervous' urine, the water increased out of proportion to the solid constituents, especially seen in the "urina hysterica," which is hardly more than simple water, often discharged in enormous quantity, at once suggests the view that impulses originating in the brain and passing down to the kidney along the vaso-dilator fibres, of whose existence evidence was given in § 413, lead to dilated blood vessels and great play of glomerular activity, without perhaps producing any other direct effect on the economy; though possibly the same emotions by constricting the cutaneous and, it may be, other vessels may raise the general blood-pressure and so help the dilated renal vessels. In the case of the urine of hysteria we are tempted, more perhaps than in any other instance, to accept the hint previously thrown out that it is possible for the vasa afferentia of the glomeruli to be alone dilated, so that the greater part of the renal blood is directed to the glomeruli and the epithelium of the tubules left in its usual quiet. But this is as yet pure speculation.

SEC. 4. THE DISCHARGE OF URINE.

§ **424**. *Structure of the ureter.* The ureter, like the large ducts of other glands, consists of an epithelium resting on a connective tissue basis strengthened with plain muscular fibres. The epithelium is in its characters intermediate between that lining the œsophagus, which as we have seen (§ 221) resembles the epidermis of the skin and that lining the ducts of the glands of the alimentary canal. It consists not of a single layer but of three or four layers of cells. The lowermost cells, next to the basement membrane which limits the connective tissue basis, are oval cells placed vertically, in one or two layers. The cells of the next layer are irregular in form and often pear-shaped, with a narrowing process dipping down between the cells below. Above these, forming the surface of the epithelium, is a layer of flat or of flattened cubical cells. All the cells are nucleated, and there are no special features in their cell-substance.

The connective tissue is, as in a mucous membrane, delicate immediately below the epithelium, but becomes coarser and more fibrous in its outer parts. The muscular fibres are arranged in three layers, an inner longitudinal, a thicker middle circular, and a thinner less regular outer longitudinal layer better developed in the lower part of the tube than elsewhere.

Nerves pass into the ureter at the upper end from the renal plexus and at the lower end from the spermatic and hypogastric plexuses, and at the two ends nerve-cells are scattered among the nerve-fibres.

The pelvis of the kidney is an expansion of the upper end of the ureter, and is lined by an epithelium like that of the ureter, which is continued into the calyces and over the projecting papillæ of the pyramids. The circular muscular fibres of the ureter are continued over the pelvis but form here a relatively thinner layer, while both longitudinal layers are very scanty and gradually become lost.

At its lower end each ureter opens by an oblique opening, serving as a valve, into the cavity of the bladder.

§ **425**. *Structure of the bladder.* The epithelium of the bladder resembles in its characters that of the ureter, but the appearances presented by the cells in sections of prepared bladders will naturally vary a good deal according as the bladder was hardened in a contracted or in a distended state. This epithelium with the underlying fine connective tissue forms a mucous membrane, separated by submucous connective tissue from a well-developed muscular coat, which in turn is invested with an outer coat of connective tissue covered, over the greater part of the organ, with peritoneum.

The well-developed, plain muscular fibre-cells which constitute this muscular coat are gathered into rounded bundles, or flattened bands, which in turn are arranged in a plexiform manner, being bound together by connective tissue carrying blood vessels and nerves. The direction of these bundles is not very regular, but they may be regarded as forming on the inner side below the mucous membrane a circularly disposed coat, better developed at the lower part of the bladder round the opening of the urethra than elsewhere, and outside this a longitudinally disposed coat, the longitudinal direction of the bundles being better seen at the front and back than at the sides. Many of the bundles and networks of bundles, however, in both coats run a course which is neither exactly longitudinal nor circular. The inner longitudinal coat of the ureter appears to be represented by a very thin and inconspicuous layer. The thicker and better developed portion of the circularly disposed coat is sometimes spoken of as the *sphincter vesicæ*, and the longitudinally disposed coat is similarly sometimes called the *detrusor urinæ*; but, as we shall see, these names are undesirable. In the dog the longitudinal bundles are much better developed than the circular; but the relative proportion of the two sets of bundles seems to vary in different animals.

The bladder is supplied with nerves from the hypogastric plexus, the fibres being both medullated and non-medullated. They appear, as in the case of the rectum (§ 276), to have a double origin, coming on the one hand from the lower dorsal and upper lumbar spinal cord through the sympathetic system, and on the other hand, in a more direct manner, from the sacral spinal nerves. More abundant round the neck of the bladder than higher up they run at first in the outer connective tissue coat, beneath the peritonæum and, forming plexuses, ultimately end partly in the blood vessels and partly in the muscular fibres, though some fibres are said to have been traced to the epithelium. Groups of nerve-cells occur on the plexuses, especially near the neck.

§ **426**. The urine, like the bile, is secreted continuously; the flow may rise and fall, but, in health, never absolutely ceases for any length of time. The cessation of renal activity, the so-called suppression of urine, entails speedy death. The minute streams passing continuously, now more rapidly now more slowly, along the collecting and discharging tubules, are gathered into the renal pelvis, whence the fluid is carried along the ureters into the bladder partly by pressure and gravity, and from time to time partly, as we have already said (§ 415), by the peristaltic contractions of the muscular walls of the ureter.

If in a living animal a ureter be laid bare and stimulated, mechanically or otherwise, at a part of its course, waves of peristaltic contraction may be seen to pass in both directions from the spot stimulated, upwards towards the kidney and downwards towards the bladder. In the absence of artificial stimulation spontaneous waves of contraction make their appearance, sometimes repeated with tolerable regularity (about every 20 seconds in the rabbit), sometimes occurring in groups with longer pauses between. These spontaneous contractions invariably pass in one direction, from the kidney to the bladder; and their frequency and vigour seem to be determined by the activity of the secretion of urine. But they are not directly called forth by the urine either mechanically distending the tube or chemically stimulating the inner surface, for regularly recurring contractions may be observed in a kidney and ureter removed from the body, or even in an isolated excised piece of the ureter.

The rhythmically repeated contractions arise spontaneously in the muscular coat of the ureter much in the same way as the similar cardiac contractions arise in the muscular substance of the heart; and it may here be mentioned, in support of what was urged in § 155 with regard to the heart-beats not being started by nerve-cells, that rhythmically repeated spontaneous peristaltic contractions have been observed in isolated pieces of ureter taken from the middle of its course, in which no nerve-cells and indeed no distinct nerve-fibres could be observed.

In the living body these spontaneous movements, beats they might be called, are subordinated to the flow of urine into the pelvis; the more active the secretion of urine the more frequent and vigorous are the beats of the pelvis and ureter; but the exact mechanism by which the secretion and the movements are maintained in harmony has not yet been cleared up.

Micturition.

§ **427**. In the urinary bladder, the urine is collected, its return into the ureters being prevented by the oblique entrance into the bladder and valvular nature of the orifices of those tubes; and its discharge from thence in considerable quantity is effected from time to time by a somewhat complex muscular mechanism, of the nature and working of which the following is a brief account.

The involuntary muscular fibres forming the greater part of the vesical walls are arranged as we have said partly in a more or less longitudinal direction, and partly in a circular manner. After it has been emptied the bladder is contracted and thrown into folds; as the urine gradually collects, the bladder becomes more and more distended. The escape of the fluid is in part prevented by the resistance offered by the elastic fibres in the walls of the urethra which help to keep the urethral channel closed. But this is not all; for observation shews that fluid is retained within the bladder up to a pressure of 20 inches of water so long as the bladder is governed by an intact spinal cord, but gives way to a pressure of 6 inches only when the lumbar spinal cord is destroyed or the vesical nerves are severed. This affords very strong evidence that the obstruction at the neck of the bladder to the exit of urine depends on some tonic muscular contraction maintained by a reflex or automatic action of the lumbar spinal cord. And it has been maintained that it is the circularly disposed fibres specially developed around the neck of the bladder which are the subjects of this tonic contraction and thus the chief cause of the retention; hence the name sphincter vesicæ. The continuity of these fibres, however, with the rest of the circular fibres of the bladder suggests that they probably do not act as a sphincter, but that their use lies in their contracting after the rest of the vesical fibres, and thus finishing the evacuation of the bladder. The resistance in question is supplied by a tonic contraction not of these circular fibres of the bladder itself but of the muscular fibres, partly plain, partly striated, surrounding the prostatic portion of the urethra, and constituting the *sphincter vesicæ externus* or *prostaticus* or sphincter of Henle. It is stated that artificially excited contractions of these fibres will resist a pressure of fluid in the bladder.

When the bladder has become full, we feel the need of making water, the sensation being heightened if not caused by the trickling of a few drops of urine from the full bladder into the urethra. We are then conscious of an effort; during this effort the bladder is thrown into a long-continued contraction of an obscurely peristaltic nature, the force of which is more than sufficient to overcome the resistance offered by the urethra, and the urine issues in a stream, the sphincter vesicæ externus being at the same time either relaxed after the fashion of the sphincter ani, or at least overcome. In its passage along the urethra, the exit of the urine, at all events of the last portions, is forwarded by irregularly rhythmic contractions of the bulbo-cavernosus or ejaculator urinæ muscle, the contractions of which compress the urethra; and the whole act is further assisted by pressure on the bladder exerted by means of the abdominal muscles, very much the same as in defæcation.

In the case of the rectum we were able (§ 276) to distinguish between the actions of the longitudinal and of the circular coats, and we said that the two coats had distinct nervous supplies (Fig. 70). The bladder has, as we have said, a similar double nerve supply, and it is very probable, but not yet distinctly proven, that this like double supply has a like double action. Stimulation of the branches coming from the sacral nerves, at the same time that it throws the longitudinal coat of the rectum into contractions brings about in the dog, in which the longitudinal fibres of the bladder are much more pronounced than the circular, powerful vesical contractions. Moreover, stimulation of the sacral nerves on one side produces unilateral contraction of the bladder. From this we may infer that the sacral nerves govern the longitudinal coat. Stimulation of the hypogastric nerves carrying fibres from the dorsal and upper lumbar cord, see Fig. 70, while throwing the circular coat of the rectum into strong contractions, gives rise to vesical contractions, but these are by no means so marked as those which appear when the sacral nerves are stimulated. We may probably conclude that the more important fibres in the fundus of the bladder, which are for the most part longitudinal, are to be regarded as governed for the most part by the sacral nerve-fibres, while the circular muscular fibres around the neck of the bladder, whose contraction completes as it were the emptying of the bladder, are those on which the hypogastric nerve-fibres have chief influence.

§ **428**. We said just now "when the bladder has become full," but this must not be understood to mean, "when the bladder has received a certain quantity of fluid." On the contrary, it is a matter of common experience that we feel the desire to make water sometimes when a large quantity and sometimes when a small quantity of urine has accumulated in the bladder. We have evidence that the bladder possesses to a very high degree that obscure continuous contraction which we speak of as 'tone'; and further that the amount of its tone is exceedingly variable, the organ, quite independently of distinct efforts at micturition, being at one time contracted and at another flaccid and distended. When it is in a contracted state, a small quantity of fluid may exert the same effect on the vesical walls as a larger quantity when the bladder is flaccid. Hence while the determining cause of the desire to make water is the pressure of the urine upon the vesical walls, the quantity needed to produce the necessary fulness is dependent on the amount of tonic contraction of the muscular fibres existing at the time. And we have evidence that this tone is regulated by the nervous system.

§ **429**. Micturition as sketched above seems at first sight, and especially when we appeal to our own consciousness, a purely voluntary act. A voluntary effort throws the muscular fibres of the bladder into contractions, an accompanying voluntary effort lessens the tone of the sphincter externus, probably by inhibiting its centre in the spinal cord, while other voluntary efforts throw the ejaculator and abdominal muscles into contractions, and, the resistance of the urethra being thereby overcome, the exit of the urine naturally follows.

There are facts, however, which prevent the acceptance of so simple a view. In the first place, in cases of urethral obstruction, where the bladder cannot be emptied when it reaches its accustomed fulness, the increasing distension sets up fruitless but powerful contractions of the vesical walls, contractions which are clearly involuntary in nature, which wane or disappear, and return again and again in a rhythmic manner, and which may be so strong and powerful as to cause great suffering. It seems that the fibres of the bladder, like all other muscular fibres, have their contractions augmented in proportion as they are subjected to tension. Just as a previously quiescent ventricle of a frog's heart may be excited to a rhythmic beat by distending its cavity with blood, so the quiescent bladder may, quite independent of the will, be excited, by the distension of its cavity, to a peristaltic action which in normal cases is never carried beyond a first effort, since with that the bladder is emptied and the stimulus is removed, but which in cases of obstruction is enabled clearly to manifest its rhythmic nature.

In the second place it has been shewn that quite normal micturition may take place in a dog in which the lumbar region of the spinal cord has been completely and permanently separated by section from the upper dorsal region. In such a case there can be no exercise of volition, and the whole process appears as a reflex action. When under these circumstances the bladder becomes full (and otherwise apparently the act fails) any slight stimulus, such as sponging the anus or slight pressure on the abdominal walls, causes a complete act of micturition: the bladder is entirely emptied, and the stream of urine towards the end of the act undergoes rhythmical augmentations due to contractions of the ejaculator urinæ. These facts can only be interpreted on the view that there exists in the lower spinal cord (of the dog) what we may speak of as a micturition centre capable of being thrown into action by appropriate afferent impulses, the action of the centre being such as to cause a contraction of the walls of the bladder and of the ejaculator urinæ, and at the same time to suspend the tone of the sphincter vesicæ externus. Clinical experience also goes to shew the existence of a similar micturition centre in man, placed higher up in the cord than the corresponding 'genital' centre governing the genital organs.

Moreover we have, in the case both of man and of other animals, experimental and other evidence that contraction of the bladder is frequently brought about by reflex action. Thus the pressure within the bladder when observed for any length of time is found to be subject to considerable and manifold variations.

Over and above passive changes in pressure due to the respiratory movements, through which the bladder is pressed upon at each descent of the diaphragm, active contractions, of a strength inadequate to bring about micturition, are from time to time observed. These in some instances appear to be spontaneous, or to be the result of emotions, but they may be readily induced in a reflex manner, by stimulating various sentient surfaces or sensory nerves. And common experience affords many instances where vesical contractions thus brought about in a reflex manner acquire strength adequate to empty the bladder.

Observations of vesical pressure may be most conveniently carried out by introducing into the bladder a catheter connected with a water manometer and a registering apparatus, and so arranged as to allow fluid to be driven into or received from the bladder at pleasure.

§ **430**. Involuntary micturition obviously of reflex nature has frequently been observed in cases of paralysis from disease of or injury to the spinal cord; and the involuntary micturition which is common in children, as the result of irritation of the penis and genital organs, and which sometimes occurs in the adult as the result of emotions, or at least sensory impressions, appears to be the result of reflex action. In these several cases we may fairly suppose that the centre in the spinal cord is affected by afferent impulses reaching it along various sensory nerves or descending from the brain. Hence we are led to the conception that when we make water by a conscious effort of the will, what occurs is not a direct action of the will on the muscular walls of the bladder, but that impulses started by the will descend from the brain after the fashion of afferent impulses and thus in a reflex manner throw into action the micturition centre in the spinal cord. We may draw an analogy between the micturition apparatus and the respiratory mechanism. We saw reasons in the latter case to think that when the will interfered with the respiratory movements, it did so by acting upon the nervous mechanism in the central nervous system and not by acting directly on the muscular fibres of the diaphragm and other respiratory muscles. And the case of the plain muscular fibres of the bladder seems even stronger than that of respiratory muscles so largely skeletal in nature. We might also draw an analogy with the heart. We are not able to throw into action, by any direct effort of the will, the cardiac augmentor mechanism. Were we able to do so powerfully and suddenly, we might throw into violent action a weakly beating heart much in the same way that we empty an obscurely contracting bladder. Nor is this view negatived by the fact that paralysis of the bladder, or rather inability to make water either voluntarily or in a reflex manner, is a common symptom of cerebral or spinal disease or injury. Putting aside the cases in which the reflex act is not called forth because the appropriate stimulus has not been applied, the failure in micturition under these circumstances may be explained by supposing that the shock of the spinal injury or some extension of the disease has rendered the spinal centre unable to act.

The so-called incontinence of urine in children is simply an easily excited and frequently repeated reflex micturition. In cases of cerebral or spinal disease a form of incontinence is frequently met with which seems to be of a different nature. The bladder becoming full, but, owing to a failure in the mechanism of voluntary or reflex micturition, being unable to empty itself by a complete contraction, a continual dribbling of urine takes place through the urethra, the fulness of the bladder being sufficient to overcome the resistance at the neck of the urethra. It is probable, however, that even in these cases the flow is partly caused by obscure, unfelt, intrinsic contractions of the bladder.

§ **431**. Whether, under normal conditions, the urine undergoes any notable change during its stay in the bladder has been much debated. Experiments shew that poisonous substances injected into the bladder with all due care to avoid any abrasion of the epithelium are absorbed and produce their usual effects. It has also been stated that if a solution of urea be injected into the bladder after ligature of both ureters, and allowed to stay for some hours, part of the urea disappears. But at present there is no very decided proof that under ordinary conditions either the water or other constituents of urine are to any appreciable extent absorbed by the bladder.

Under abnormal conditions, as in inflammation or irritation of the bladder, the urine may have undergone marked changes during its stay in the bladder, one of the most common being a change of some of the urea into ammonium carbonate, by which the urine becomes alkaline. Under abnormal conditions also, the mucus of the urine, which in a healthy man is insignificant, though in some animals, for instance the horse, it occurs in considerable quantity, is largely increased during the stay in the bladder. Since there are in man no goblet cells in the vesical epithelium (in the frog they are present) or mucus glands in the walls of the bladder, this mucus must be supplied by an abnormal metabolism of the ordinary epithelial cells.

SEC. 5. THE STRUCTURE OF THE SKIN.

§ **432**. The skin, like a mucous membrane, consists of an epithelium resting upon a connective tissue basis; the epithelium, which is composed of many layers of cells, is called *epidermis*, the connective tissue basis is called *dermis*, or *corium*, or *cutis vera*. The surface of the dermis is thrown up into a number of elevations, *papillæ*, which differ in size, form, complexity and arrangement in different regions of the body. Some are small, more or less conical elevations, *simple papillæ*. In others, a broader primary elevation is divided at its summit into a number of secondary elevations; these are *compound papillæ*. In many regions of the skin, as for example in the palms of the hands, the papillæ are arranged in ridges separated by shallow furrows. The surface of the skin, that is, the contour of the epidermis, does not follow the papillary contour of the dermis; the papillæ accordingly appear to plunge into and to be covered up by the more even epidermis, the surface of which, however, is marked by the ridges and furrows spoken of above as well as by bolder creases and folds.

The surface of the dermis is not developed into a distinct and separable basement membrane, as is so often the case in a mucous membrane; but in the most superficial portions of the dermis the connective tissue shews little or no fibrillation and consists of a homogeneous matrix, in which are imbedded connective tissue corpuscles and extremely fine elastic fibres. This superficial portion of the dermis, which is especially well-developed in the papillæ, serves accordingly the purposes of a basement membrane, and sharply defines the dermis from the overlying epidermis. At a very little distance from the epidermis fibrillation makes its appearance, the bundles of fibrillæ interlacing in a network which, very close set in the outer, more superficial layers, becomes more and more open in the inner, deeper parts. The connective tissue of the dermis thus passes insensibly into the sub-cutaneous connective tissue, in which thick interwoven bundles of fibrillæ, bearing in transverse section a certain resemblance to sections of tendon-bundles, form a tough open network, the larger spaces of which are frequently occupied by masses of fat cells of the subcutaneous adipose tissue. Elastic fibres are very abundant in the dermis proper, being very fine immediately beneath the epidermis and becoming coarser in the deeper parts; they are present also, though to a less extent, in the subcutaneous connective tissue. The skin as a whole is a very elastic structure.

Blood vessels are very abundant, forming close set capillary networks and loops immediately under the epidermis, especially in the papillæ, and more open networks elsewhere; but no blood vessel passes into the epidermis. Lymphatic vessels and lymphatic capillaries are abundant in the dermis, being connected here as in other regions of the body with smaller "lymph-spaces."

The consideration of the nerves of the skin it will be advantageous to defer until we come to deal with the skin as an organ of sense; for though some of the cutaneous nerve fibres are efferent fibres distributed to the blood vessels, and probably to the sweat-glands and other structures not directly connected with the sense of touch, by far the greater number are afferent fibres beginning in distinct tactile organs, or otherwise serving as sensory structures.

§ **433**. The epidermis consists of two parts, separated by a fairly sharp line of demarcation: an inner soft layer, the Malpighian layer, or *stratum Malpighii*, and an outer harder horny layer, or *stratum corneum*. The skin as is well known varies in thickness in different regions of the body, and the differences are due almost exclusively to variations in the thickness of the horny layer which, as over the lips, may be extremely thin, or as on the heel, excessively thick; compared with the variations in thickness of the horny layer, the variations in thickness of the Malpighian layer or of the dermis may be disregarded.

The line of demarcation between the Malpighian and horny layers follows the contour of the surface of the skin, not that of the dermis, the papillæ of which appear in sections as if imbedded in the Malpighian layer. When the skin after death is macerated, the horny layer is apt to peel off from the Malpighian layer below, which, originally soft and rendered still softer by the maceration, then appears as a layer of slimy tissue spread out between the sides of and covering the summits of the papillæ of the dermis, somewhat after the fashion of a network; hence this layer was in old times spoken of as the *rete mucosum*.

The lowermost, innermost portion of the Malpighian layer resting upon the dermis, consists of a single layer of elongated, or almost columnar cells placed vertically, that is with their long axis perpendicular to the plane of the dermis. This layer, which preserves the original features of the epiblast of the embryo, and which may be followed over the papillæ as well as along the intervening valleys, presents a characteristic appearance in vertical sections of the skin. Each cell, which is about as large as a leucocyte, about 12μ by 6μ, consists of a relatively large oval nucleus lying in the midst of a coarsely granular cell-substance, which stains readily with the ordinary staining reagents. The base of the cell abutting on the dermis often shews fine processes interlocking with corresponding processes from the dermis; the sides of the cells are in close contact, but merely in contact, no cement substance existing between them.

The rest of the cells of the Malpighian layer, much like each other, are polygonal or irregularly cubical cells, resembling the vertical cells just spoken of in so far that each consists of a coarsely granular cell-substance in which is imbedded a relatively large nucleus; this however is spherical not oval. The surface of each cell is thrown up into short ridges, radiating somewhat irregularly from the centre of the cell and projecting at the surface and edges, so as to give the cell somewhat the appearance of being armed with a number of prickles. Hence these cells are often called 'prickle cells.' The prickles of a cell do not interlock with those of its neighbours but touch at their points, so that the contact of two adjacent cells is not complete but carried out by the points of the prickles only, minute spaces being left between. Hence the whole Malpighian layer is traversed by a labyrinth of minute passages, along which fluid can pass between the touching prickles.

In dark skins, as in that of the negro, pigment particles abound in the lower Malpighian cells, especially in the vertical layer. In such cases branched pigment-cells, connective tissue corpuscles loaded with pigment granules, are to be seen in the dermis also; and occasionally similar branched cells may be seen in the epidermis between the Malpighian cells. Leucocytes also not infrequently pass out of the dermis and wander among the cells of the Malpighian layer.

The nuclei not only of the vertical but also of the other polygonal cells may, not unfrequently, be observed in various stages of karyomitosis. Throughout life the cells of this Malpighian layer of the skin appear to be undergoing multiplication by division; the increase of population thus arising is kept down by the cells passing upwards and outwards, and becoming transformed into the cells of the horny layer.

§ **434**. The line of demarcation between the Malpighian layer and the horny layer is, as we have said, sharp and distinct. It is furnished by two peculiar strata of cells, more conspicuous in some regions of the skin than in others. The lowermost, innermost stratum consists of a single layer or of two or three layers of cells which are not unlike Malpighian cells, but are differentiated by their form, being extended horizontally so as frequently to appear fusiform in vertical sections, by the absence of prickles, by their staining very deeply with certain reagents, such as osmic acid, and especially by their cell substance being crowded with large discrete granules of a peculiar nature. Hence this stratum is called the *stratum granulosum.*

The stratum above this consists of one or two or even more layers of cells, elongated and flattened horizontally, the cell substance of which is homogeneous and transparent, free from granules and not staining very readily. In the middle of a cell may frequently be seen a rod-shaped nucleus placed horizontally. These clear transparent cells form a transparent seam, the *stratum lucidum*, between the stratum granulosum and Malpighian layer below and the horny layer above.

§ **435**. The horny layer, which is as we have said of variable but nearly always of considerable thickness, is formed of a number of layers of cells which, differentiated already in the lowest layers, have that differentiation completed as these pass upwards. The upper, outer portion of this horny layer is continually being shed or rubbed off in the form of flakes of variable size. Each flake upon examination, as for instance after dissociation by maceration or with the help of alkalis, is found to be composed of elements which can no longer be recognized as cells, and which may be spoken of as scales. Each scale is a flattened mass or plate in which no nucleus can be seen, and which consists not of the proteids and other constituents of ordinary cell substance (§ 29) but almost exclusively of a material called *keratin.* This is a body, the exact nature of which has not yet been clearly made out, but which has the general percentage composition of proteids, from which it is a derivate, with the exception that it contains a considerable quantity of sulphur (the keratin of hair contains as much as 5 p.c.); this sulphur appears to be somewhat loosely attached to the other elements of the keratin since it may be removed by boiling with alkalis.

The lowermost portions of the horny layer are composed of elements which may still be recognized as cells, inasmuch as each contains a nucleus, though this is obviously undergoing change and on the way to disappear. Each cell is, however, flattened and plate-like, and its substance already consists largely of keratin. In passing upwards from the lower to the more superficial parts of the horny layer such an imperfect cell loses its nucleus, and becomes the wholly keratinous plate just described. The whole horny layer consists of strata of elements, horny to begin with, but becoming more completely so in the upper parts. Below, in contact with the moist Malpighian layer, the horny layer is moist but the superficial parts become dry by evaporation; and here the strata delaminate from each other, the outer ones, as we have said, being shed in the form of flakes, which seen in the dry condition under the microscope have often the appearance of irregular fibres.

The karyomitosis seen in the cells of the Malpighian layer, not only in those of the vertical layer but in the others as well, shew, as we have said, that these multiply by division; we have no evidence of multiplication taking place elsewhere in the epidermis. The more superficial cells of the Malpighian layer, thrust upwards by the new comers, are transformed into the cells of the stratum granulosum; and although we do not as yet fully understand the exact nature of the transformation we may conclude that the peculiar granules of these cells are concerned in the manufacture of keratin. Changed by the consumption of their granules in this manufacture the cells of the stratum granulosum become first the cells of the stratum lucidum and then the cells of the distinctly horny layer, pushed upwards through which by the new formations continually succeeding below them, they pass to the surface and are eventually shed.

§ **436**. *The sweat-glands.* A sweat-gland, like other glands, consists of a secreting portion and a conducting portion. The secreting portion is a long tubular alveolus coiled up in a knot and placed in the subcutaneous connective tissue at some distance from the epidermis. Generally the gland is formed of one such tubule only, but sometimes two tubules unite into a common duct. The duct beginning in the knot, in the convolutions of which it shares, runs a somewhat wavy but otherwise straight course vertically towards the surface of the skin on to which its lumen opens.

Through the epidermis the duct is nothing more than a tubular passage excavated out of the epidermis with a remarkable corkscrew course, the turns of the screw becoming more open and the canal wider in the upper part as it approaches the surface. In the Malpighian layer the cells bordering on the passage are flattened and inclined downwards so as to afford a more or less definite lining; there is a similar arrangement but not so well seen in the corneous layer. Reaching the dermis, in a valley between papillæ, the passage becomes a regular duct, with an independent epithelium of its own, a distinct basement membrane continuous with the upper surface of the dermis, and an outer coat of connective tissue strengthened, in the case of some of the larger glands, such as those of the axilla, with plain muscular fibres. The epithelium consists of two or three layers of small rounded cells, each with a relatively large but absolutely small nucleus, generally staining deeply. The cells leave a narrow tubular thread-like lumen which is lined with a very characteristic distinct cuticle.

The duct continues to possess these characters after it has entered the knot and begun to pursue a twisted course, but soon changes suddenly into the secreting tubule. This may be distinguished from the duct by being wider, and by being lined by a single layer of cubical or columnar cells larger than those of the duct, bearing larger nuclei, and behaving differently towards various staining reagents. The lumen though fairly distinct is not lined by any cuticle as in the duct. Lying between the basement membrane and the epithelial cells, or rather imbedded in the basement membrane, are seen a number of plain muscular fibres disposed longitudinally or in an elongated spiral, and often forming a distinct coat beneath the epithelium.

As in the case of other glands, we are unable to make any statement as to the work carried on by the epithelium lining the duct, but we may probably assume that the sweat is mainly secreted by the larger cells of the terminal coiled part of the tubule. These cells therefore like other secreting cells are probably 'loaded' and 'discharged'; but as yet no marked structural changes in the cells corresponding to these phases have been satisfactorily ascertained, though after the administration of pilocarpine, which causes sweating, the cells of glands hardened in alcohol stain more deeply than usual with carmine. It must be remembered, however, that the sweat contains normally neither mucus nor proteid substances, and we should therefore not expect to observe 'granules' in the cells.

The peculiarly placed muscular fibres have been supposed, by their contraction, to assist in the flow of sweat along the tubule. In certain cutaneous glands of the frog, of a relatively simple nature, there is evidence that the secretion is ejected from the comparatively large lumen by the contraction of plain muscular fibres in the wall of the gland, or by a contraction of the wall itself, which is contractile without being distinctly differentiated into muscular tissue. And this rather supports the above view; but the matter is at present by no means clear.

The coil of a sweat-gland is well supplied with blood vessels in the form of capillary networks, and nerves have been traced to the tubes; but the exact manner in which these end is not as yet known.

Though present in all regions of the skin (of man), the sweat-glands are unequally distributed, being more abundant in some regions, such as the palms of the hand, than in others. In the axilla are glands of very large size, and in these the ducts possess distinctly muscular coats.

§ **437**. *Sebaceous glands.* These are appendages of the hairs. A hair is a development, in the form of a cylinder, of a cap of corneous epidermis surmounting a papilla of the dermis sunk to the bottom of a tubular pit, or involution of the skin, called a hair follicle. In the upper part of the hair follicle the walls consist of ordinary skin with all its parts, dermis, Malpighian layer and corneous layer, the latter as usual of considerable thickness. At some little distance from the mouth of the follicle the corneous layer suddenly ceases, and in the follicle below this the epidermis is represented by the Malpighian layer, now called the outer root-sheath, and two layers of peculiar cells, forming the inner root-sheath, of which the outer is called Henle's and the inner Huxley's layer; these may perhaps be considered as corresponding to the stratum granulosum and lucidum respectively. The dermis of the wall of the follicle is at the same time developed into an outer layer with bundles of connective tissue disposed chiefly longitudinally, and an inner layer of peculiar nature, the arrangement of which is transverse, and which at least simulates, if it really be not, a muscular transverse coat. Between this dermis of the follicle and the outer root-sheath or Malpighian layer is a very conspicuous definite hyaline basement membrane, so thick that it presents a very easily recognized double contour.

At the bottom of the follicle the dermis of the wall of the follicle is continuous with the substance of the (dermic) papilla, while the outer root-sheath or Malpighian layer which here becomes extremely thin, and reduced to one or two layers, is reflected over the papilla, and there expands again into a mass of cells, which like the cells of the Malpighian layer in the rest of the skin multiply, and by their multiplication give rise to the corneous body of the hair. It is said that in those hairs which possess a medulla the vertically disposed lowermost cells of the Malpighian layer are at the actual summit of the papilla continued upwards in the axis of the hair, as the medulla.

The layer of Henle, following the Malpighian layer or outer root-sheath on which it rests, is similarly reflected and forms over the hair a single layer of flat transparent imbricated scales known as the cuticle of the hair. Huxley's layer, similarly reflected, forms a similar layer of similar scales, but this is considered as belonging to the root-sheath and is called the cuticle of the root-sheath.

Just where the corneous layer abruptly leaves off in the upper part of the hair follicle, a sebaceous gland opens into the cavity of the follicle on each side of the hair. Each gland consists of a short rather wide duct which divides into a cluster of somewhat flask-shaped alveoli. The basement membrane, both in the alveoli and in the duct, is lined with a layer of rather small cubical cells continuous with the layer of perpendicularly disposed cells which form the innermost layer of the outer root-sheath as of the Malpighian layer of the skin generally. This layer of cells leaves a wide lumen both in the alveoli and in the duct; this lumen, however, is occupied not as in other glands with fluid, but with cells. Both alveoli and duct in fact are filled with rounded or polygonal cells which may be regarded as modified cells of the Malpighian layer. The whole gland indeed is a solid diverticulum of the Malpighian layer.

In the alveoli the cells next to the layer of cells immediately lining the basement membrane, though larger than these, resemble them in so far that each consists of ordinary cell-substance surrounding a nucleus of ordinary character. The more central cells are different; their cell-substance is undergoing change, numerous granules or droplets, some of them obviously of a fatty nature, make their appearance in them, and the nuclei are becoming shrunk and altered. The cells are manufacturing fatty and other bodies and depositing the products in their own substance, which however is not being renewed but is dying. These changes are still more obvious in the cells lying within the duct; the cells as indicated by the breaking up of the nuclei are dead, and the whole of the cell-substance has been transformed into the material constituting the secretion of the gland, called *sebum*, which is discharged on to the surface of the skin through the mouth of the hair follicle.

In these sebaceous gland secretion, if we may continue to use the word, takes place after a fashion different from that which we have hitherto studied. In an ordinary gland the cells lining the walls of the alveoli manufacture material which they discharge from themselves into the lumen to form the secretion, their own substance being at the same time renewed so that the same cell may continue to manufacture and discharge the secretion for a very prolonged period without being itself destroyed. In a sebaceous gland the work of the cells immediately lining the wall of an alveolus appears limited to the task of increasing by multiplication. Of the new cells thus formed while some remain to continue the lining and to carry on the work of their predecessors, the rest thrust towards the centre of the alveolus are bodily transformed into the material of the secretion, and during the transformation are pushed out through the duct by the generation of new cells behind them. The secretion of sebum in fact is a modification of the particular kind of secretion taking place all over the skin, and spoken of as shedding of the skin. It is chiefly the chemical transformation which is different in the two cases. In the skin generally the protoplasmic cell-substance of the Malpighian cells is transformed into keratin, in the sebaceous glands it is transformed into the fatty and other constituents of the sebum. Some perhaps may hesitate to apply the word secretion to such a process as this; but as we shall see later on, the formation of milk, which certainly deserves to be called a secretion, is a process intermediate between the secretion of saliva and gastric juice and the formation of sebum.

The so-called 'ceruminous' glands of the external meatus of the ear are essentially sweat-glands. They are wrongly named, since the fatty material spoken of as 'wax' of the ear is secreted not by them but by the sebaceous glands belonging to the hairs of the meatus, or by the general epidermic lining. The ceruminous glands appear at most to supply the pigment which colours the 'wax.'

The Meibomian glands of the eyelids, on the other hand, are essentially the sebaceous glands of the eyelashes, the glands of Mohl being in turn sweat-glands.

SEC. 6. THE NATURE AND AMOUNT OF PERSPIRATION.

§ **438**. The quantity of matter which leaves the human body by way of the skin is very considerable. Thus it has been estimated that while ·5 gram passes away through the lungs per minute, as much as ·8 gram passes through the skin. The amount, however, varies extremely; it has been calculated, from data gained by enclosing the arm in a caoutchouc bag, that the total amount of perspiration from the whole body in 24 hours might range from 2 to 20 kilos; but such a mode of calculation is obviously open to many sources of error.

Of the whole amount thus discharged, part passes away at once as watery vapour mixed with volatile matters, while part may remain for a time as a fluid on the skin; the former is frequently spoken of as *insensible*, the latter as *sensible* perspiration or sweat. The proportion of the insensible to the sensible perspiration will depend on the rapidity of the secretion in reference to the dryness, temperature and amount of movement of the surrounding atmosphere. Thus, supposing the rate of secretion to remain constant, the drier and hotter the air, and the more rapidly the strata of air in contact with the body are renewed, the greater is the amount of sensible perspiration which is by evaporation converted into the insensible condition; and conversely when the air is cool, moist, and stagnant, a large amount of the total perspiration may remain on the skin as sensible sweat. Since, as the name implies, we are ourselves aware of the sensible perspiration only, it may and frequently does happen that we seem to ourselves to be perspiring largely, when in reality it is not so much the total perspiration which is being increased as the relative proportion of the sensible perspiration. The rate of secretion may, however, be so much increased, that no amount of dryness, or heat, or movement of the atmosphere, is sufficient to carry out the necessary evaporation, and thus the sensible perspiration may become abundant in a hot, dry air. And practically this is the usual occurrence, since certainly a high temperature conduces, as we shall point out presently, to an increase of the secretion, and it is possible that mere dryness of the air has a similar effect.

The amount of perspiration given off is affected not only by the condition of the atmosphere, but also by the circumstances of the body. Thus it is influenced by the nature and quantity of food eaten, by the amount of fluid drunk, by the character of exercise taken, by the relative activity of the other excreting organs, more particularly of the kidney, by mental conditions and the like. Variations may also be induced by drugs and by diseased conditions. How these various influences produce their effects we shall study immediately.

The fluid perspiration, or sweat, when collected, is found to be a clear colourless fluid of a distinctly salt taste, with a strong and distinctive odour varying according to the part of the body from which it is taken. Besides accidental epidermic scales, it contains no structural elements.

Sweat, as a whole, is furnished partly by the sweat-glands and partly by the sebaceous glands, for as we shall see the small amount which simply transudes through the epidermis, apart from the glands, may be neglected. Now the secretions from these two kinds of glands differ widely in nature, and the characters of the sweat as a whole will vary according to the relative proportion of the two kinds of secretion. The secretion of the sebaceous glands appears to be fairly constant, the larger variations of the total sweat depending chiefly on the varying activity of the sweat-glands. Hence when sweat is scanty, the constituents of the sebum influence largely the characters of the sweat; when on the contrary the sweat is very abundant, these may be disregarded and the sweat may be considered as the product of the sweat-glands.

We are not able, at present, to make a complete statement as to what bodies occur exclusively in the sebum and what in the secretion of the sweat-glands. The former consists very largely of fats and fatty acids, and appears to contain some form or forms of proteids; but we have reason to think that the sweat-glands secrete in small quantity some forms of fat, and especially volatile fatty acids.

When sweat is scanty, the reaction is generally acid, but when abundant, is alkaline; and when a portion of the skin is well washed the sweat which is collected immediately afterwards is usually alkaline. From this we may infer that the secretion of the sweat-glands is naturally alkaline, but that when mixed sweat is acid, the acidity is due to fatty (or other) acids of the sebum. In the horse, which is singular among hair-covered animals for its frequent profuse sweating, the sweat is said to be always acid, and to contain a considerable quantity of some form of proteid. These features are probably due to the large admixture of sebum from the numerous sebaceous glands connected with the hairs.

Taking ordinary sweat, such as may be obtained by enclosing the arm in a bag, we may say that, in man, the average amount of solids is from 1 to 2 p. c., of which about two-thirds consist of organic substances. The chief normal constituents are: (1) Sodium chloride, with small quantities of other inorganic salts. (2) Various acids of the fatty series, such as formic, acetic, butyric, with probably propionic, caproic, and caprylic. The presence of these latter is inferred from the odour; it is probable that many various volatile acids are present in small quantities. Lactic acid, which has been reckoned as a normal constituent, is stated not to be present in health. (3) Neutral fats, and cholesterin; these have been detected even in places, such as the palms of the hand, where sebaceous glands are absent. (4) The evidence goes to shew that neither urea nor any ammonia compound exists in the normal secretion to any extent, though some observers have found a considerable quantity of urea (calculated at 10 grms. in the 24 hours for the whole body). Apparently some small amount of nitrogen leaves the body by the skin as a whole, but this is probably supplied by the sebum or by the epidermis.

In various forms of disease the sweat has been found to contain, sometimes in considerable quantities, blood, albumin, urea (particularly in cholera), uric acid, calcium oxalate, sugar (in diabetic patients), lactic acid, indigo (or indigo-yielding bodies giving rise to 'blue' sweat), bile and other pigments. Iodine and potassium iodide, succinic, tartaric, and benzoic (partly as hippuric) acids have been found in the sweat when taken internally as medicines.

Cutaneous Respiration.

§ 439. A frog, whose lungs have been removed, will continue to live for some time; and during that period will continue not only to produce carbonic acid, but also to consume oxygen. In other words, the frog is able to breathe without lungs, respiration being carried on efficiently by means of the skin. In mammals and in man this cutaneous respiration is, by reason of the thickness of the epidermis, restricted to within very narrow limits; and indeed it has been questioned whether it can be spoken of at all as a true respiration. When the body remains for some time in a closed chamber to which the air passing in and out of the lungs has no access (as when the body is enclosed in a large air-tight bag fitting tightly round the neck, or where a tube in the trachea carries air to and from the lungs of an animal placed in an air-tight box), it is found that the air in the chamber loses oxygen and gains carbonic acid. The amount of carbonic acid which is thus thrown off by the skin of an average man in 24 hours amounts to about 10 grms., or according to some observers to (no more than) about 4 grms., increasing with a rise of temperature, and being very markedly augmented by bodily exercise.

It is stated that the amount of oxygen consumed is about equal in volume to that of the carbonic acid given off, but some observers make it rather less. It may be doubted, however, whether the carbonic acid comes direct from the blood; it may come from decompositions taking place in the sweat, of carbonates for instance. Similarly the oxygen which disappears may be simply used in oxidizing some of the constituents of the sweat. It is evident that the loss which the body suffers through the skin consists, besides a small quantity of sodium chloride, chiefly of water.

When an animal, a rabbit for instance, is covered over with an impermeable varnish such as gelatine, so that all exit or entrance of gases or liquids by the skin is prevented, death shortly ensues. This result cannot be due, as was once thought, to arrest of cutaneous respiration, seeing how insignificant and doubtful is the gaseous interchange by the skin as compared with that by the lungs. Nor are the symptoms at all those of asphyxia, but rather of some kind of poisoning, marked by a very great fall of temperature, which however seems to be the result not of diminished production of heat, but of an increase of the discharge of heat from the surface. The animal may be restored, or at all events its life may be prolonged with abatement of the symptoms, if the great loss of heat which is evidently taking place be prevented by covering the body thickly with cotton wool, or keeping it in a warm atmosphere. The symptoms have not as yet been clearly analysed, but they seem to be due in part to a pyrexia or fever possibly caused by the retention within or reabsorption into the blood of some of the constituents of the sweat, or by the products of some abnormal metabolism, and in part to a dilation of the cutaneous vessels caused by the application of varnish; owing to the dilated condition of the cutaneous vessels the loss of heat through the skin is abnormally large, even though the varnish may not be a good conductor.

§ **440**. *Absorption by the skin.* Although under normal circumstances the skin serves only as a channel of loss to the body, it has been maintained that it may, under particular circumstances, be a means of gain; and the little which we have to say on this matter may perhaps be said here. Cases are on record where bodies are said to have gained in weight by immersion in a bath, or by exposure to a moist atmosphere during a given period, in which no food or drink was taken, or to have gained more than the weight of the food or drink taken; the gain in such cases must have been due to the absorption of water by the skin. Direct experiments, however, throw doubt on these statements, for they shew that under ordinary circumstances such a gain by the skin is slight, being apparently due to mere imbibition of water by the upper layers of the epidermis.

Absorption of various substances takes place very readily by abraded surfaces where the dermis is laid bare or covered only by the lowest layers of epidermis, but it has been debated whether substances in aqueous solution can be absorbed by the skin when the epidermis is intact, the evidence on this point being contradictory. In the case of the skin of the frog an absorption of water and of various soluble substances certainly takes place. In the case of the sound human skin there are no *à priori* reasons why water carrying substances dissolved in it should not pass inwards through the corneous as well as the other layers of the epidermis, the amount so passing depending, among other things, upon the condition of the skin; and common experience seems to shew that it does. Nevertheless the results of actual experiment are conflicting. Some observers maintain that soluble non-volatile substances are not absorbed, and that volatile substances such as iodine which may be detected in the system after a bath containing them are absorbed not by the skin but by the mucous membrane of the respiratory organs, the substance making its way to the latter by volatilisation from the surface of the bath. Others again have found evidence of absorption, especially with volatile substances, even when care has been taken to avoid all errors; and the greater weight may perhaps be given to these since they accord with common experience. The conflict of experimental results, however, at least shews that we do not fully understand the conditions under which such absorption takes place.

There is moreover evidence that even solid particles can pass through an intact skin. The lymphatics in the skin of a newborn infant have been found crowded with the particles of the peculiar fatty secretion which covers the skin at birth; and solid particles rubbed into even the sound skin may, especially when applied in a fatty vehicle, as *ex. gr.* in the well-known mercury-ointment, find their way into the underlying lymphatics. The wandering leucocytes which are at times found among the epidermic cells may perhaps take part in this transport.

SEC. 7. THE MECHANISM OF THE SECRETION OF SWEAT.

§ **441**. In dealing with the manner in which various circumstances affect the amount of sweat secreted we may, as we have already said, consider the sweat as a whole to be supplied by the sweat-glands alone. For though it seems evident that some amount of fluid must pass by simple transudation through the ordinary epidermis of the portions of skin intervening between the mouths of the glands, yet on the whole it is probable that the portion which so passes is a small fraction only of the total quantity secreted by the skin; and direct experiment shews that even the simple evaporation of water is much greater from those parts of the skin in which the glands are abundant than from those in which they are scanty. We have as yet no evidence that the sebaceous glands vary in activity; their very peculiar form of secretion, if we may speak of it as a secretion, is not adapted to sudden changes, and at all events we have as yet no evidence that circumstances rapidly and largely modify the amount of sebum discharged by healthy sebaceous glands.

The secreting activity of the skin, like that of the other glands, is usually accompanied and aided by vascular dilation. In one of the early experiments on division of the cervical sympathetic, it was observed that in the case of the horse, the vascular dilation of the face on the side operated on was accompanied by increased perspiration. Indeed the connection between the state of the cutaneous blood vessels and the amount of perspiration is a matter of daily observation. When the vessels of the skin are constricted, the secretion of the skin is diminished; when they are dilated, it becomes abundant. In this way, as we shall later on point out, the temperature of the body is largely regulated. When the surrounding atmosphere is warm, the cutaneous vessels are dilated, the amount of sweat secreted is increased, and the consequently augmented evaporation tends to cool down the body. On the other hand, when the atmosphere is cold, the cutaneous vessels are constricted, perspiration is scanty, and less heat is lost to the body by evaporation.

The analogy with the other secreting organs which we have already studied leads us, however, to infer that there are special nerves directly governing the activity of the sudoriparous glands, independent of variations in the vascular supply. And not only is this view suggested by many facts, such as the profuse perspiration of the death agony, of various crises of disease, and of certain mental emotions, and the cold sweats occurring in phthisis and other maladies, in all of which the skin is anæmic rather than hyperæmic, but we have direct experimental evidence of a nervous mechanism of perspiration as complete as the vasomotor mechanism.

If in the cat[1] the peripheral stump of the divided sciatic nerve be stimulated with the interrupted current, drops of sweat may readily be observed to gather on the hairless sole of the foot of that side. The sweating is not due to any increase of blood-supply, for it may be observed when the cutaneous vessels are thrown into a state of constriction by the stimulus, or even when the aorta or crural artery is clamped previous to the stimulation, and indeed may be obtained by stimulating the sciatic nerve of a recently amputated leg. Moreover when atropin has been injected, the stimulation produces no sweat, though vaso-motor effects follow as usual. The analogy between the sweat-glands of the foot and such a gland as the submaxillary is in fact very close, and we are justified in speaking of the sciatic nerve as containing secretory fibres distributed to the sudoriparous glands of the foot. Similar results may be obtained with the nerves of the fore limb. And in ourselves a copious secretion of sweat may be induced by tetanizing through the skin the nerves of the limbs or the face.

If a cat in which the sciatic nerve has been divided on one side be exposed to a high temperature in a heated chamber, the limb the nerve of which has been divided remains dry, while the feet of the other limbs sweat freely. This result shews that the sweating which is caused by exposure of the body to high temperatures is brought about by the agency of the central nervous system, and not by a local action on the sweat-glands; for the foot of the limb whose nerve has been divided is equally exposed to the high temperature. A high temperature it is true up to a certain limit increases the irritability of the epithelium of the sweat-glands and predisposes it to secrete, just as it promotes action in the case of a muscle or nerve or other forms of living substance. Thus stimulation of the sciatic in the cat produces a much more abundant secretion in a limb exposed to a temperature of 35° or somewhat above, than in one which has been exposed to a distinctly lower temperature, and in a limb which has been placed in ice-cold water hardly any secretion at all can be gained; but apparently mere rise of temperature without nerve-stimulation will not give rise to a secretory activity of the glands. The sweating caused by a dyspnœic condition of blood, and such appears to be the sweat of the death agony, is similarly brought about by the agency of the central nervous system. When an animal with the sciatic nerve divided on one side is made dyspnœic, no sweat appears in the hind limb of that side, though abundance is seen in the other feet.

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[1] The cat sweats freely in the hairless soles of the feet but not on any part of the body covered with hairs. The dog also sweats in the same regions but not so freely as the cat; indeed sweating is often absent, the ducts being stopped by growth of the corneous epidermis. Rabbits and other rodents appear not to sweat at all. The snout of the pig sweats freely; and the often profuse sweating of the horse, a singular event among hair-covered animals, is known to all.

Sweating may be brought about as a reflex act. Thus when the central stump of the divided sciatic is stimulated sweating is induced in the other limbs, and in ourselves the introduction of pungent substances into the mouth will frequently give rise to a copious perspiration over the side of the face. We are thus led to speak of sweat centres, analogous to the vaso-motor centres, as existing in the central nervous system; and as in the case of vaso-motor centres, a dispute has arisen as to whether there is a dominant sweat centre in the medulla oblongata or whether such centres are more generally distributed over the whole of the spinal cord.

It does not at present appear certain whether the sweating caused by heat is carried out by direct action of the heated blood on the sweat centres, or by the higher temperature stimulating the skin and so sending up afferent impulses which produce the effect in a reflex manner; but in the case of dyspnœa at least we may fairly suppose that the action of the venous blood is chiefly if not exclusively on the nerve centres. Some drugs, such as pilocarpin, which cause sweating, appear to produce their effect chiefly by a local action on the glands, since the action continues after the division of the nerves (though pilocarpin apparently has as well some slight action on the nerve centres), and the antagonistic action of atropin is similarly local. Picrotoxin and strychnia appear to produce their sweating action chiefly if not exclusively by acting on the central nervous system, while nicotin seems to act both centrally and peripherally.

§ **442**. The sweat-fibres for the hind foot (in the cat) appear to leave the spinal cord by the roots of the lower dorsal and upper lumbar nerves, pass along the *rami communicantes* to the abdominal sympathetic, and thus reach the sciatic nerve. They thus follow very much the course of the vaso-constrictor fibres of the lower limb; but the particular spinal nerves by which the sweat-fibres issue from the cord have not yet been definitely settled, and possibly they are in the dog and cat the last two or the last three dorsal and first two or four lumbar nerves. Similarly the sweat-nerves for the fore-foot leave the spinal cord by the roots of some of the upper (chiefly the fourth, but possibly also the fifth, and sixth) dorsal nerves, pass into the thoracic sympathetic, thence into the ganglion stellatum, and so join the brachial plexus by the fine branches passing from the ganglion to the spinal nerves. The course to the fore-foot is finally along the median and ulnar nerves respectively. In the horse the sweat-fibres for the side of face and in the pig those for the snout appear to run in branches of the fifth nerve and not in the facial; in the latter animal at least some of these fibres reach the fifth nerve from the cervical sympathetic, but apparently not all.

§ **443**. The fact mentioned above that in the horse, after section of the cervical sympathetic nerve on one side of the neck, profuse sweating is apt to break out on that side of the face, has suggested the idea that this nerve conveys inhibitory impulses to the sweat-glands of the head and face, and that when it is divided the sweat-fibres running in the fifth nerve, having nothing to counteract them, set up sweating. But it is probably sufficient in this case to suppose that the glands predisposed to activity by the higher temperature brought about by the section of the sympathetic dilating the blood vessels, are more easily excited by any stimulus working upon them through the fifth nerve. And though the idea of a double nervous mechanism, augmenting and inhibitory, governing the activity of the sweat-glands, is a tempting one, there are at present no satisfactory reasons for adopting it.

CHAPTER IV.

THE METABOLIC PROCESSES OF THE BODY.

§ **444**. We have followed the food through its changes in the alimentary canal, and have seen it enter into the blood, either directly or by the intermediate channel of the lacteals, in the form of peptone (or otherwise modified albumin), sugar (lactic acid), and fats, accompanied by various salts and water. We have further seen that the waste products which leave the body are urea, carbonic acid, salts and water. We have now to attempt to connect together the food and the waste products; to trace out as far as we are able the various steps by which the one is transformed into the other. There remains the further task to inquire into the manner in which the energy set free in this transformation is distributed and made use of.

The master tissues of the body are the muscular and nervous tissues; all the other tissues may be regarded as the servants of these. And we may fairly presume that, besides the digestive and excretory tissues which we have already studied, many parts of the body are engaged either in further elaborating the comparatively raw food which enters the blood, in order that it may be assimilated with the least possible labour by the master tissues, or in so modifying the waste products which arise from the activity of the master tissues that they may be removed from the body as speedily as possible. There can be no doubt that manifold intermediate changes of this kind do take place in the body; but our knowledge of the matter is at present very imperfect. In a few instances only can we localize these metabolic actions and speak of distinct metabolic tissues. In the majority of cases we can only trace out or infer chemical changes, without being able to say more than that they do take place somewhere; and in consequence, perhaps somewhat loosely, speak of them as taking place in the blood.

How little we know concerning the metabolism of the master tissues themselves was shewn when we were dealing with these tissues in an earlier part of this work; but success in the study of these can hardly be expected until our knowledge is increased as regards the changes which the blood undergoes before it reaches and after it leaves the muscle or the nerve. The fact that a large part of the absorbed food is carried through the liver before it is thrown on the general circulation leads us to suppose that in this large organ important metabolic processes are carried on; and observation with experiment confirms this view. Important as the secretion of bile may be the other metabolic functions of the liver are of still greater importance; and preparatory to the study of these we may now take up the structure of this organ.

SEC. 1. THE STRUCTURE OF THE LIVER.

§ **445**. The liver is a gland, the conducting portion of which, the bile-duct or gall-duct, after repeated division ends in passages lined by secreting structures; but the comparatively simple arrangement seen in other glands in which the terminal ducts or ductules end in blind, tubular or flask shaped alveoli is, in the liver, modified and to a certain extent obscured. These modifications may be ascribed on the one hand to the fact that the cells which provide the secretion, being also engaged as we have just said in important metabolic duties, are developed out of proportion to the biliary passages, and on the other hand to the fact that the ordinary vascular supply of an artery (hepatic artery) ending through capillaries in a vein (hepatic vein), is overshadowed by the great portal system; the great and wide vena portæ divides into venous capillaries, and these are gathered up again into the hepatic vein, which thus draws its main supply of blood from it rather than from the much smaller hepatic artery.

The whole liver, invested with a capsule of connective tissue and marked out into its several lobes, is divided by septa of connective tissue into a number of small primary units of somewhat polygonal form, called *lobules*, each being in mass about the size of a pin's head. The distinctness of a lobule from its neighbours depends on the relative abundance of the connective tissue which separates them; and this is much more conspicuous in some animals (such as the pig) than in others (such as the rabbit or man).

The large portal vein, the much smaller bile-duct and the still smaller hepatic artery, entering the liver together on its under surface at the *porta hepatica*, or gate of the liver, are invested with a considerable quantity of connective tissue, carrying also lymphatics and nerves, which is continuous with the connective tissue covering of the whole liver and is called Glisson's capsule. Rapidly dividing, the divisions continuing to run together side by side in the beds of connective tissue into which Glisson's capsule is continued, the three vessels ultimately reach the outsides of the several lobules, the septa of connective tissue defining the lobules from each other being the terminations of Glisson's capsule carrying the three sets of vessels. The small branches of the portal vein thus reaching the surface of the lobules, and running and anastomosing freely between the lobules, are spoken of as *interlobular* veins. Thus each lobule is provided, at different parts of its circumference, with two, three or more interlobular veins, accompanied in a manner which we shall describe by divisions of the bile-duct and hepatic artery, all being embedded in a (variable) quantity of connective tissue.

Each lobule at one part of its circumference rests directly, with the intervention of hardly any connective tissue at all, upon a small vein which is not part of the portal vein, but which when traced out is found to pass into and form the hepatic vein; it is called a *sublobular* vein. A lobule in fact, though generally polyhedral as seen in sections of the liver, may be considered as somewhat of the form of a broad inverted flask, the neck of which rests directly on a sublobular branch of the hepatic vein, and upon the polygonal body of which, surrounded by more or less connective tissue, abut at various points interlobular branches of the portal vein.

§ **446**. The network of interlobular veins surrounding the circumference of a lobule gives origin to a number of rather wide capillary vessels which run in a radial direction towards the middle of the lobule; these are connected by cross capillaries, which however are shorter and less abundant than the radial capillaries, so that the meshes are elongated, more or less rectangular spaces converging radially towards the centre of the lobule. Towards the middle of the lobule the capillaries merge into a single vein, called an *intralobular* vein, which, running down the neck of the flask, and receiving the capillaries of the neck as it goes, falls into the sublobular vein spoken of above.

The elongated meshes of this capillary network converging radially towards the intralobular vein at its beginning in the body of the flask-like lobule and as it is continued along the neck of the flask, are occupied by relatively large polygonal nucleated cells, which we shall presently describe in detail as *hepatic cells.* The width of a mesh is generally such as to admit one or two cells abreast, but its length admits several cells; hence the cells are arranged in narrow radiating broken columns converging towards the middle of the lobule.

The columns of cells and the meshwork of capillaries practically constitute the whole of the lobule, for besides a minimum of connective tissue forming an adventitia to the capillaries, certain lymphatic passages afforded by this adventitia, and extremely minute passages which form the beginnings of the bile-ducts, and of which we shall speak later on, nothing else is present. The lobule in fact consists first of a vascular framework of capillaries which, taking origin at the surface of the lobule from the interlobular portal veinlets, are disposed in a network with meshes elongated in a radial direction, and converge at the centre of the lobule to form the intralobular veinlet falling into the sublobular (hepatic) vein, and secondly of radiating columns of cells filling up the radiating meshes of this vascular network. Hence in a section of a hardened and prepared uninjected liver, in which the blood vessels are largely emptied, the areas of the sections of lobules are indicated by the radially converging columns of cells, and (according to the animal employed) are more or less distinctly marked out by the septa of connective tissue, in which may be seen here and there the lumina of the larger interlobular veins. In lobules, in which the section has passed through the middle of the lobule, the lumen of the central intralobular vein will also be visible; but often the section will cut a lobule so superficially as to miss the intralobular vein altogether; and it is only when the section happens to pass through the middle of the lobule in the plane of the long axis of the flask, that the origin of the intralobular vein in the middle of the body of the flask and its course along the neck to the sublobular vein is displayed.

§ **447**. If the section be extensive enough there may be seen here and there sections of the portal vein, hepatic artery and bile-duct running in Glisson's capsule. Sections of the branches of the hepatic vein formed by the union of sublobular veins may also be seen. These may be recognised by the absence or by the extreme scantiness of any connective tissue wrapping to the vein, even in the case of the larger branches. The wall of the vein too is very thin and consists of hardly more than the tunica intima resting on a thin connective tissue basis, muscular fibres being so very scanty that the tunica media may be said to be absent.

The walls of the portal vein on the contrary are thick and muscular; the trunk is more abundantly supplied with muscular fibres than any other vein in the body; and the branches within the liver are, in diminishing degree, thick and muscular. This is intelligible when it is remembered that the blood is distributed into capillaries from the portal vein as from an artery; and indeed it has been maintained that the portal vein is subject to rhythmic contractions of its walls, as if to assist in the passage onward of the blood. Neither in the trunk nor in the branches are any valves present, and these are also absent from the branches of the hepatic vein.

The branches of the hepatic artery are very much smaller than the branches of the portal vein, and even much smaller than the branches of the bile-duct in company with which they run. As they proceed in their course they supply the walls of the portal veins and of the bile-ducts and the substance of Glisson's capsule, and eventually discharge their blood into the portal veinlets. It has been maintained that some of the finer branches run directly into the vascular meshwork of the marginal parts of the lobules, but this is disputed.

§ **448**. *The Bile-ducts.* The larger bile-ducts, namely, the hepatic duct leading from the liver, the cystic duct leading from the gall-bladder, and the common bile-duct formed by the junction of the two, have the ordinary characters of large gland-ducts. An epithelium of columnar cells rests on a connective tissue basis, and so constitutes a mucous membrane; this is supported by a well-developed muscular coat, consisting of a thicker internal layer of circularly disposed, and a thinner external layer of longitudinally disposed, plain muscular fibres mixed up with a good deal of connective tissue. The walls of the gall-bladder have essentially the same structure. Both the gall-bladder and the ducts are capable of carrying out peristaltic contractions of their walls, by the help of which when needed (§ 252*) the rapid flow of bile into the intestine is secured.

The bile-ducts within the liver are also similarly constituted, their walls of course becoming thinner and less muscular as the tubes diminish in size, and the epithelium becoming cubical rather than columnar. A characteristic feature of the smaller bile-ducts as they run in Glisson's capsule is that, unlike the ducts of most glands, they form frequent anastomoses.

The epithelium of the ducts contains many goblet cells, and in the walls of the larger ducts and of the gall-bladder small mucous glands are present; in the smaller ducts these are apt to be simplified into mere pits or short depressions of the mucous membrane.

The small terminal anastomosing bile-ducts, now consisting of hardly more than a cubical epithelium resting on a connective tissue basis, may be traced to various points of the margin of a lobule and there seem to end abruptly. Just before a bile-duct thus ends or seems to end, the cubical cells become much flatter, the lumen of the tube however remaining narrow; and then the end of the tube seems blocked up with the hepatic cells of the lobule. To understand, however, the nature of this peculiar ending we must return to the hepatic cells.

§ **449**. The hepatic cells filling up the meshes of the vascular network of a lobule are relatively large (20 to 30μ in diameter in man) polygonal or roughly cubical cells. Each contains a relatively large rounded nucleus, and in not a few cells two nuclei may be seen. Each cell is partly in contact with its neighbours, and partly abuts on a blood vessel; for there is probably not a cell in a lobule which is not in touch, for some part of its surface, with one or more blood vessels. Where the surfaces of two cells meet their substances are in contact, that is to say, there is no cement substance between them, and the external layer of cell-substance, though it may at times at all events differ from the more internal cell-substance, is not differentiated into a distinct membrane or cuticle. Where the surface of a cell abuts on a blood vessel the substance of the cell is generally separated from the wall of the vessel by a lymph-space, which is connected with the hepatic lymphatic vessels.

The cell-substance itself, as might be expected from what has been already urged concerning the metabolism going on in the liver, presents appearances which differ very widely according to circumstances. Sometimes the cell-substance appears dense, compact and of fairly uniform texture though more or less granular; the whole cell is then of relatively small bulk. Sometimes the cell-substance appears large and bulky, owing to its being largely loaded with a substance staining red-brown with iodine, which we shall study in detail presently, called glycogen. When such a cell is hardened and the glycogen dissolved out, the cell-substance appears to be so completely riddled with vacuoles, as to be reduced to a mere shell surrounding a loose irregular network except immediately round the nucleus, where it is more solid. But it will be best to reserve the discussion of these changes in the cells until we have studied to some extent the metabolic changes which take place in the liver. We may add however that very frequently, especially in certain animals, the hepatic cell is crowded with oil globules of various sizes; these are at times so numerous as completely to hide the nucleus, which cannot be seen until the fat has been removed.

§ **450**. Where the sides of two hepatic cells are in contact, careful examination with high powers of the microscope will often reveal, at about the middle of the line of junction of the two sides, a minute hole, a tenth or less of the diameter of the cell, which according to some observers is lined with a delicate cuticular lining. This hole is the section of a minute canal passing between the two cells in the middle line of their apposed surfaces. A model of it might be made on two small blocks of chalk by cutting a narrow semicircular groove down the middle of one side of each block, and then bringing these two sides into accurate contact.

We have already said (§ 416) that the blue colouring matter, sodium sulphindigotate, when injected into the veins is excreted by the liver as well as by the kidney. If the animal be killed at an appropriate time after the injection and the liver hardened and prepared, sections of the liver will, in successful specimens, reveal a close set network of blue thin lines traversing the whole of each of the lobules. The meshes of the network are of about the width of a hepatic cell; and upon examination it will be found that the empty minute holes, just spoken of as seen in the sections of a liver prepared in the ordinary way, are now filled with the blue pigment; the minute canal of which each hole is a section is a part of a network of minute canals, passing between the cells in various directions all over the lobule. They may be traced to the edge of the lobule, and at various points of the margin the blue line between the hepatic cells will be seen to be continuous with a larger quantity of the same blue material occupying the lumen of one of the minute bile-ducts as it abuts on the margin of the lobule. These minute canals are therefore continuous with the bile-ducts; they are the terminations of the bile-ducts within the lobules, and indeed not only may they be injected during life with sodium sulphindigotate, but injection material may, though with difficulty, be driven into them backwards along the bile-ducts. They are spoken of as *bile-capillaries*; the name perhaps is not a very desirable one, but it has been generally adopted.

We said just now that each hepatic cell touched a blood vessel by at least one of its surfaces, we may now add that each hepatic cell has at least one side, and generally more than one side, grooved to form a bile-capillary. Since each side thus grooved is in contact with the corresponding side of a neighbouring cell, it cannot run alongside a blood vessel. Hence between a bile-capillary and a blood vessel some amount of cell-substance is always interposed. The relative position of the bile-capillaries and blood vessels may be illustrated by taking a cube and converting it into a polygon by bevelling down the angles of the sides, leaving in the first instance those of the upper and lower faces untouched. The blood vessels may then be considered as running down the bevelled edges, while bile-capillaries run along the middle lines of the sides. Two such cubes placed end to end might represent a thin small islet of cells in one of the smaller shorter radial meshes of the vascular network; and then the angles of the upper and lower face of the conjoined cubes would have also to be bevelled for the cross bars of the network. Frequently, as we have said, the cells lie two abreast in a mesh of the vascular network; then of course in the model the angles of the surfaces in contact would not have to be bevelled since no blood vessels run between them. If several such bevelled cubes were built up into a model, it would be seen that the network of bile-capillaries runs along the middle of the surfaces between the blood vessels, forming nodal points where cells are in contact with each other by their surfaces, and leaving some amount of cell-substance between the bile-capillary and the blood vessels. This at least may be taken as the typical arrangement, when the network of bile-capillaries is most complex. But many cells have the lumen of a bile-capillary on one side only; and occasionally a bile-capillary is seen in section at the point of convergence of three cells after the fashion of an ordinary alveolus.

When a bile-duct abuts on the margin of a lobule the lumen, as we have previously said, seems suddenly to come to an end. The flattened cells lining the ductule or terminal portion of the duct suddenly change into large hepatic cells, marginal cells of the lobule, which appear to be completely in contact with each other and to block up the ductule. But along the sides of these marginal cells as of all the other cells of the lobule run bile-capillaries, and these are continuous on the one side with the lumen of the ductule, and on the other hand with the network of the bile-capillaries traversing the lobule. In the ductule itself the lumen is single, cylindrical, and of some size, it suddenly divides into much smaller passages, and the cells lining these smaller branching passages are no longer simply epithelium cells lining a duct, but complex hepatic cells.

It would appear then that after all the hepatic cells are really cells lining the terminal secreting portions of the duct, lining we might almost say the alveoli, but owing on the one hand to the distribution of blood vessels, so different from that which obtains in the alveoli of other glands, and on the other hand to modifications of the hepatic cells, due to their being engaged in other functions than that of secreting bile, the relations of the cells to the lumina of the alveoli is peculiar.

§ 451. In the lower animals the structure of the liver is simpler, and a brief description of the frog's liver may perhaps assist towards the comprehension of the nature of the mammalian liver. The liver of the frog as seen in a section appears to be

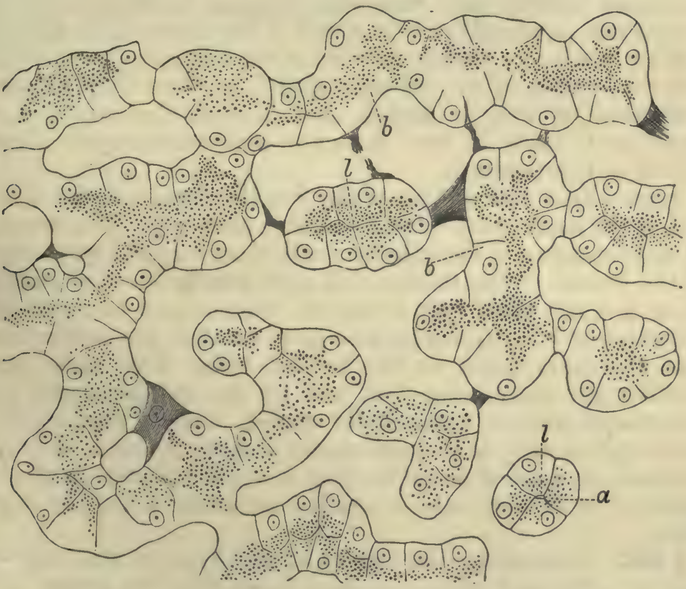

FIG. 91. SECTION OF LIVER OF FROG. (Langley.)

The Figure shews the tubular structure of the liver. At (*a*) a tubule is seen in transverse, at (*b*) in longitudinal section. *l*, lumen of tubule.

The liver was that of a winter frog, and the cells shew an inner zone of proteid granules; the outer zone was chiefly occupied by glycogen.

made up of a number of tubules, which repeatedly not only branch but also anastomose (Fig. 91), and among which run the capillary blood vessels uniting the branches of the portal with those of the hepatic vein. There is no very obvious division into lobules; indeed in a section of small area the tubules appear to run irregularly; nevertheless they have a definite arrangement around the branches of the hepatic vein. Both longitudinal and transverse sections of one of these tubules shew that it is lined with large wedge-shaped cells, leaving a very narrow, almost linear but still distinct lumen. Around the tubule is disposed a network of capillaries, and, as in the alveolus of an ordinary gland, the blood vessel is separated from the lumen of the tubule by the thickness of an entire cell. Each cell possesses a rounded nucleus which lies in the outer part of the cell nearer to the blood vessel than to the lumen; and we may mention here, though we shall return to the point later on, that the cell-substance contains a number of granules which are sometimes scattered throughout the cell and sometimes aggregated near the lumen. The hepatic cell of the frog repeats in fact the main characters of the secreting cell of an ordinary gland, of a pancreatic cell for example. The tubules moreover when traced are found to end in ducts, the (secreting) hepatic cells suddenly changing to cubical and then to columnar (conducting) cells, which in the larger ducts bear cilia. In other words, the hepatic tubules of the frog are alveoli, differing from the alveoli of an ordinary gland, in that they repeatedly anastomose as well as branch, and in that the lumen is very narrow and, since it also branches and anastomoses, forms a network of fine passages.

From a liver such as that of the frog the change to the arrangement of the mammalian liver is one of degree only. The branching and anastomosing of the tubules is still more frequent and complete and the lumina of the tubules still narrower, so much so that each cell, as it were, takes part in several tubules, and the network of the lumina or bile-capillaries is so close set that the meshes are of about the same width as the hepatic cells. The blood vessels moreover are more abundant, and by the establishment of an arrangement whereby interlobular (portal) veinlets send capillaries to converge radially to an intralobular (hepatic) veinlet, the hepatic substance, instead of as in the frog being distributed more or less uniformly, is divided into a number of small areas, the hepatic lobules.

§ **452**. Concerning the nerves of the liver we shall say what there is to be said when we come to consider the action of the nervous system on the hepatic metabolic processes.

With lymphatics the liver is well provided. Within the lobule lymph-spaces exist between the walls of the vascular network and the outer margins of the hepatic cells, and at the circumference of the lobule these spaces open into definite lymphatic vessels which run in the connective tissue separating the lobules and forming the beginnings of Glisson's capsule. The lymphatic vessels lying near the upper surface of the liver find their way along the ligaments of the liver to the thoracic lymphatics, those coming from the right side passing to the right lymphatic trunk; all the rest of the lymphatics pass out along the portal canal and fall into the abdominal thoracic duct.

From the details given above we may infer that the liver is in part an ordinary secreting gland. The hepatic cells living on the blood brought to them manufacture bile, which they discharge into the narrow lumina of the minute bile-capillaries, from whence it flows outside the lobule along the more open passages of the bile-ducts. But the blood supply is not only out of all proportion to the demands of mere secretory work, but also is peculiar in so far that the blood reaches the liver laden with many of the products of digestion. This would lead us to infer that the hepatic cells are, as we have already suggested, also largely engaged in withdrawing substances from the portal blood, not for the purpose simply of forming bile, but in order that other substances, or the same substances more or less altered should be added to the blood of the hepatic vein and so distributed throughout the body for the body's use. And we have experimental evidence that such a work is carried on.

SEC. 2. THE HISTORY OF GLYCOGEN.

§ **453**. If the liver of a well-fed animal be removed immediately after death, rapidly divided into small pieces, thrown into boiling water, rubbed up and boiled, a decoction may be obtained which after careful neutralisation and filtration will be tolerably free from proteid matter. Such a decoction is remarkably opalescent, milky in fact in appearance, much more so than a similar decoction from muscle or other tissue, and remains opalescent even after repeated filtration. Treated with iodine, the solution turns a brownish red, port-wine red colour, not unlike that given by dextrine when iodine is added; the colour disappears on warming, but reappears on cooling provided that not too much proteid matter has been left in the solution. Treated with Fehling's fluid or other tests for sugar, the solution is found to contain a small and variable, but only a small, quantity of sugar.

If the solution be exposed, preferably in the warm, to the action of saliva or of some other amylolytic ferment, or be boiled with dilute acid, the opalescence disappears; and the now clear transparent solution gives no longer the port-wine reaction with iodine. Tested moreover with Fehling's fluid or by other means it is now found to contain a considerable quantity of sugar.

If alcohol be added to the opalescent solution until the mixture contains 60 p.c. of the alcohol (previous concentration by evaporation being desirable) a white amorphous precipitate is thrown down. This precipitate, removed by filtration, boiled with an alcoholic solution of potash in which it is insoluble, but which dissolves and destroys any proteids which may be present, treated with ether to remove fatty impurities, and washed with alcohol may be obtained in a pure condition. It then appears as a white amorphous powder, fairly soluble in water, but always giving rise to a milky opalescent solution unless an excess of alkali be present, in which case the opalescence may be slight or absent.

The opalescent solution of this purified material gives a port-wine reaction with iodine, but no reaction whatever with Fehling's fluid or the other sugar tests. Treated with an amylolytic ferment or boiled with dilute acid, the solution, like the raw decoction of liver, loses its opalescence and its port-wine reaction with iodine but now gives abundant evidence of the presence of sugar, dextrose, if boiling with acid has been employed, maltose chiefly, if an amylolytic ferment has been used. If quantitative determinations be employed it will be found that the amount of sugar obtained is proportionate to the amount of the white powder acted upon; in other words the substance forming an opalescent solution is converted into sugar, the solution of which is clear. Obviously the substance is a body allied to starch; and this is confirmed by its elementary composition, which is found to be $C_6H_{10}O_5$ or some multiple of this.

Hence this body is called *glycogen*. And it is obvious from what has been stated above, that the liver of a well-fed animal at the moment of death contains a considerable quantity of glycogen either in a free state or in such a condition that it is set free by subjecting the liver to the action of boiling water. We may add that it occurs in the liver in the hepatic cells, for the reaction of a port-wine colour given under certain conditions by the hepatic cells, § 449, is due to the presence of glycogen in them.

§ **454**. If the liver, instead of being treated immediately upon the death of the animal, is allowed to remain in the body of the dead animal for several hours, especially in a warm place, before a decoction is made of it, the decoction will be found to have little or no opalescence, to be quite or nearly quite clear, to give little or no port-wine reaction with iodine, but to contain a very considerable quantity of sugar. As we said above, the decoction even of a liver taken immediately after death generally contains some little sugar, and the quantity of sugar in the liver appears as a rule to increase steadily after death, the amount of glycogen diminishing at the same time. The rapidity of the diminution of glycogen and the rate of increase of sugar vary much under various circumstances. Moreover, the decrease of the one and the increase of the other are not always strictly proportional; and indeed some observers have insisted that there is no relation between the two processes. Nevertheless, the broad fact remains that if the liver of the same well-fed animal be divided into two halves, as soon as possible after death, and one half thrown into boiling water immediately, while the other half is left, exposed to some little warmth for several, say 24 hours, the decoction of the first half will contain much glycogen and little sugar, while that of the second half will contain little glycogen and much sugar; and this fact may be taken, until the contrary is proved, to shew that the glycogen present in the liver at the moment of death is gradually after death by some action or other converted into sugar.

The action is that of some agency whose activity is destroyed by the temperature of boiling water; hence the directions repeatedly given above to throw the liver into boiling water. This naturally suggests the presence in the liver of an amylolytic ferment. But, not only have attempts to isolate from the liver an amylolytic ferment failed, in the hands of most observers at least, but the exact nature of the sugar which appears shews that the change is not affected by an ordinary amylolytic ferment. In the case of the amylolytic ferment of saliva, pancreatic juice, intestinal juice, and indeed of all other amylolytic animal fluids, the sugar into which starch or glycogen is converted is maltose. Now the sugar which appears in the liver after death is dextrose, identical, as far at least as can at present be made out, with ordinary dextrose. We are led therefore to infer that the change of glycogen into sugar which appears to go on after death is carried out by some action of the liver, probably of the hepatic cell itself, which is done away with by a temperature of 100° C., but which is not the action of a ferment capable of being isolated.

§ **455**. We have used above the phrase 'well-fed' animal because the amount of glycogen present in the liver of an animal at any one time is very variable, and especially dependent on the amount and nature of the food previously taken. When all food is withheld from an animal, the glycogen in the liver diminishes, rapidly at first, but more slowly afterwards. Even after some days' starvation a small quantity is frequently still found; but in rabbits, at all events, the whole may eventually disappear.

If an animal, after having been starved until its liver may be assumed to be free or almost free from glycogen, be fed on a diet rich in carbohydrates or on one consisting exclusively of carbohydrates, the liver will in a short time be found to contain a very large quantity of glycogen. Obviously the presence of carbohydrates in food leads to an accumulation of glycogen in the liver; and this is true both of starch and of dextrin and of the various forms of sugar, cane, grape and milk sugar. The effect may be quite a rapid one, for glycogen has been found in the liver in considerable quantity within a few hours after the introduction of sugar into the alimentary canal of a starving animal.

If an animal, similarly starved, be fed on an exclusively meat diet a certain amount of glycogen is found in the liver. This appears to be especially the case with dogs (probably with other carnivorous animals also); and in earlier works on the subject the constant presence of glycogen in the livers of dogs fed on meat was regarded as an important indication of the formation within the body of non-nitrogenous from nitrogenous material. But in the first place, the quantity of glycogen thus stored up in the liver as the result of a meat diet, is much less than that which follows upon a carbohydrate diet; and in the second place, ordinary meat, especially horse-flesh on which dogs in such experiments are usually fed, contains in itself (§ 62) a certain amount either of glycogen or some form of sugar. Moreover when animals are fed not on meat but on purified proteid, such as fibrin, casein or albumin, the quantity of glycogen in the liver becomes still smaller, though according to most observers remaining greater than during starvation. We may infer therefore that part of the glycogen which appears in the liver after a meat diet is really due to carbohydrate materials present in the meat. Part, however, would appear to be the result of the actual proteid food; and we have similar evidence that gelatine taken as food leads to the formation of some glycogen in the liver. But in this respect these nitrogenous substances fall far short of carbohydrate material.

With regard to fats, all observers are agreed that these lead to no accumulation of glycogen in the liver; an animal fed on an exclusively fatty diet has no more glycogen in its liver than a starving animal.

Hence of the three great classes of food-stuffs, the carbohydrates stand out prominently as the substances which taken as food lead to an accumulation of glycogen in the liver. We may remark that the greatest accumulation of glycogen is effected not by a pure carbohydrate diet, but by a mixed diet rich in carbohydrates. A quantity of carbohydrate mixed with a certain proportion of proteid gives rise to a larger amount of glycogen in the liver than the same quantity of carbohydrate given by itself; and it is possible that the presence of an appropriate quantity of fat still further assists the accumulation. But this result probably depends, in part at least, on the fact that, though differences may be met with in different animals, a mixture of the several classes of food-stuffs is more readily digested resulting in more nutritive material being thrown upon the blood, than is a meal consisting exclusively of one kind of food-stuff alone.

As far as we know at present the glycogen which thus appears in the liver as the result of feeding either with any of the various forms of carbohydrates, or with proteids, or with other substances, is of the same kind and presents the same characters; at least we have no evidence to the contrary.

The storing-up of glycogen in the liver is also influenced by other circumstances than the taking of food. For instance in the frog an increase of glycogen takes place during the winter months. In the summer months the liver of a frog will be found to contain very little glycogen, Fig. 92 C, unless the animal has been unusually well fed; whereas a liver examined in mid winter, Fig. 92 A, will be found to contain a considerable quantity, even though no food has been taken for months. In such a case the material for the formation of the glycogen in the liver must have been furnished by some part of the body of the frog, and could not, as may be the case when a meal leads immediately to an increase of glycogen, be supplied directly from the food. It seems as if in the summer the frog lives up to its capital of hepatic glycogen, spending it as fast almost as it is made, but that during the winter a quantity is funded to provide for the demands of late winter and early spring.

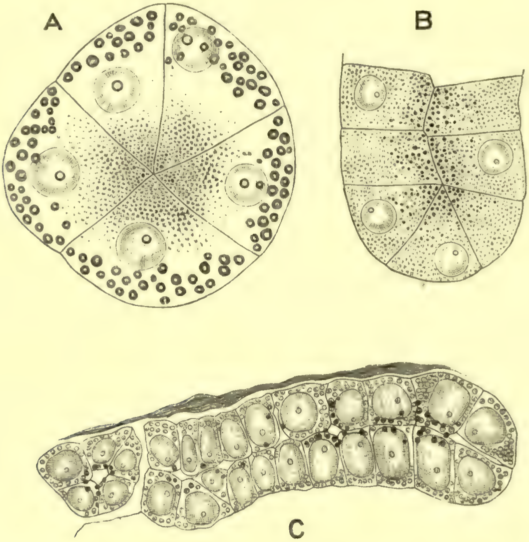

Fig. 92. Three phases of the Hepatic Cells of the Frog. (Langley.)

A. Cells rich in glycogen. Taken from a frog during winter. The cells are large, and proteid granules are massed round the lumen, the homogeneous outer zones of the cells being largely composed of glycogen which was present in considerable abundance. The outer zones contained numerous fat globules, shewn as dark dots; but as stated in the text these fat globules vary much.

B. Cells poor in glycogen. Taken from a winter frog which had been kept at 22° C. for 10 days. The cells contain very little glycogen and the proteid granules are dispersed throughout the cell. In a summer frog well fed on proteids the cells would present a very similar appearance.

C. Starved cells. Taken from a summer frog after a long fast. The cells are small and almost free from glycogen. The proteid granules are dispersed throughout the cell.

All the specimens were hardened in 1 p.c. osmic acid, and are drawn to the same or nearly to the same scale.

This winter storage of hepatic glycogen in the frog seems closely dependent on temperature. If a winter frog, whose liver is presumably more or less loaded with glycogen, be exposed for some time to a temperature of 20° or a little higher, the liver will afterwards be found to contain little or no glycogen, Fig. 92 B; and conversely if a summer frog be exposed to untimely cold, glycogen, though not in any great quantity, begins to be stored up in the liver.

§ **456**. Before we attempt to discuss further how food and other circumstances thus affect the glycogen in the liver, it will be desirable to take up the matter which we left on one side in § 449, viz. the consideration of the histological changes occurring in the hepatic cells, under various conditions. It will be convenient to begin with the cells of the more distinctly tubular gland of the frog.

In a frog which has not been subjected to any special treatment the cell-substance of the hepatic cell (cf. Fig. 92 A) will generally be found to contain lodged in itself three kinds of material, the presence of which, if not directly recognisable in the fresh cell, may be demonstrated by the use of various reagents. In the first place, oil globules of variable size and in variable amount are scattered throughout the cell; sometimes, as we have already said, these are extremely abundant; but there is otherwise nothing very special about these fat globules in the hepatic cell to demand any discussion concerning them apart from the general discussion on the formation of fat, into which we shall enter later on.

In the second place, a number of small discrete granules may be seen lodged in the cell-substance. These appear to be of a proteid nature and are generally most abundant on the inner side of the cell near the lumen of the bile passage. The presence of these granules is closely dependent on the activity of the digestive processes. They diminish when digestion is going on and accumulate again afterwards. Putting aside certain details we may say that these granules behave very much like the granules in an albuminous salivary cell, a pancreatic cell or a chief gastric cell; and we may probably safely conclude that they, like the granules in these cells, are in some way concerned in the formation of the secretion; that is, in their case, bile.

In the third place, the cell contains more especially in its outer parts nearer the blood vessel, away from the lumen of the bile passage, a variable quantity of material which differs from the ordinary cell-substance in being hyaline and refractive and hence glassy looking, and in staining port-wine red with iodine instead of brownish yellow as does ordinary cell-substance. This material is, though with some little difficulty, soluble in water, and by this means may be dissolved out from the cell. When this is done the places which it occupied appear as vacuoles or gaps of various sizes limited by bars of the cell-substance, which thus takes on the form of a network, the meshes of which are wider and more conspicuous in the outer part of the cell, in which the hyaline material was previously most abundant. In the inner part of the cell where the hyaline material was scanty the cell-substance is more dense, and even in the outer part a shell of more dense, less reticulate cell-substance affords a definite outline to the cell. There can be no doubt that this hyaline material is either actual glycogen such as may be extracted from the liver, or, as seems more probable from its deficient solubility, glycogen in some more or less loose combination with some other body, a combination, however, of such a kind that the iodine reaction makes itself felt.

§ **457**. The above may be taken as a general description of a cell in an ordinary condition. The question now comes before us, What changes are brought about by various foods or by the absence of food?

If a frog be largely fed on a diet containing large quantities of carbohydrates, the liver will be found rich in glycogen and the cells will present the following characters. The cell is relatively large (cf. Fig. 92 A) and as it were swollen; the cell-substance is largely occupied by the hyaline material just spoken of, especially in its outer parts, so that in sections prepared and mounted in the ordinary way in which the glycogen has been dissolved out the greater part of the cell consists of a loose open network of bars of stained cell-substance, with wide meshes; a certain quantity of more solid, generally granular looking cell-substance occupies the part of the cell nearest the lumen, and a thin shell of cell-substance forms an envelope for the rest of the cell. The nucleus is large and distinct, but though changes in the nucleus accompanying changes in the cell-substance have been described, they are not sufficiently important to detain us now. When such a cell is seen in a perfectly fresh state, the hyaline refractive material (which we need hardly say gives a marked reaction with iodine) often hides the nucleus and the greater part of the cell-substance proper.

If on the other hand the frog be fed on a proteid diet free from carbohydrates, for instance on fibrin, the liver contains little or no glycogen, and the hepatic cells are not only much smaller but present an appearance very different from the above (cf. Fig. 92 B). Little or no hyaline material is visible, the cells give little or no port-wine reaction with iodine, but only the usual brown yellow proteid reaction, and in specimens prepared and mounted in the ordinary way the cell-substance appears densely granular throughout.

Lastly, if the frog be starved, and if to the effects of starvation there be added those of exposure to a high temperature (25°), by which as we have seen the hepatic cells are markedly affected, the liver is found to be free from glycogen, and the hepatic cells to be extremely small (cf. Fig. 92 C), only half the size or even less, of those of the well-fed frog, but otherwise much like the cells in a frog fed on proteid material.

§ **458**. In the mammal changes in the hepatic cells similar to those just described as occurring in the frog have also been observed. When the animal is fed on a diet rich in carbohydrates, and when therefore as we have seen the liver abounds in glycogen, the hepatic cells (Fig. 93) are larger (so large that they have by some authors been described as compressing the lobular capillaries) and loaded with the same refractive hyaline material staining port-wine red with iodine. When this material is dissolved out a coarse open network of cell-substance is displayed. The most marked point of difference between the mammalian and frog's hepatic cell under these conditions is that in the former, the hyaline, glycogenic substance is gathered at first centrally round the nucleus (not more on the outer side as is the case in the frog) and spreads from the centre towards the periphery, always leaving on the extreme outside a somewhat thick shell of cell-substance, which in hardened and prepared specimens may strikingly simulate a thickened cell-wall. We may add that in an animal thus fed the whole liver is very large and as it were swollen; it is also soft and tears easily.

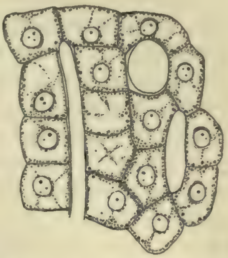

FIG. 93. SECTION OF MAMMALIAN LIVER RICH IN GLYCOGEN. (Langley.)

Osmic acid specimen, glycogen not dissolved out.

In an animal fed on proteids alone, for instance on fibrin, the liver frequently contains some glycogen and the hepatic cells contain a small quantity of hyaline glycogenic material. As in the corresponding case in the frog, the cells are comparatively small, and the cell-substance appears finely and uniformly granular.

In a starved mammal, the liver is small, dense to the touch and tough; it contains a trace only of glycogen or none at all; the cells (Fig. 94) are small, as it were shrunken, and the cell-substance, which gives no port-wine reaction, or a mere trace only, with iodine, is still more finely granular.

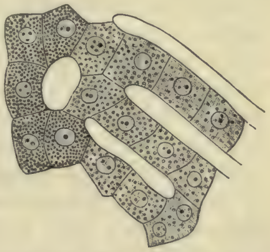

FIG. 94. SECTION OF MAMMALIAN LIVER, CONTAINING LITTLE OR NO GLYCOGEN. (Langley.)

Osmic acid specimen. The granules are not well preserved in some of the cells.

§ 459. The microscopic appearances just described shew, and indeed general considerations lead us to the same conclusion, that the processes taking place in a hepatic cell are very complex. In the first place the constituents of bile are being formed and discharged into the bile passages after the fashion of an ordinary secreting gland. In the second place, a formation of glycogen is also taking place, and we shall have presently to consider briefly the relations of the one process to the other. In the third place, as is especially indicated by the somewhat peculiar effects on the hepatic cell of food exclusively proteid in nature, other processes, similar perhaps to the formation of glycogen but not resulting in the storage of any carbohydrate material and dealing possibly with proteid substances, also take place. Hence the exact interpretation of all the changes which may be observed becomes exceedingly difficult.

Leaving the processes of the first and third kind wholly on one side for the present, and confining our attention entirely to the glycogen, it is obvious that the hepatic cell manufactures the glycogen in some way or other, and lodges it in its own substance for the time very much in the way that a secreting cell manufactures and lodges in itself for a time material for the secretion which it is about to pour forth. There is this difference, that in the one case the material of the secretion, after undergoing as we have seen more or less change, is cast out into the lumen of the alveolus, whereas in the other case the glycogen, which must undergo change since it may be made to disappear rapidly from the hepatic cell, is not when changed cast out into the bile passages; it must therefore be sent back again to the blood.

§ **460**. We say "manufactures the glycogen in some way or other," and we have now to inquire what we know concerning the nature and the several steps of this manufacture.

We have already seen that the presence of glycogen in the liver is especially favoured by a carbohydrate diet; and in our studies on digestion we have seen reason to think that a very large part at all events of the carbohydrate material of a meal is absorbed as sugar by the capillaries of the intestine and carried as sugar to the liver in the portal blood. Hence, it seems only reasonable to conclude that the glycogen which makes its appearance in the liver after an amylaceous meal arises from a direct conversion of the sugar carried to the liver by the portal vein, the sugar becoming through some action of the hepatic cell-substance dehydrated into glycogen, or animal starch as it has been called, the process being a reverse of that by which in the alimentary canal starch is hydrated into sugar through the action of the salivary and pancreatic ferments. Vegetable cells can undoubtedly convert both starch into sugar and sugar into starch; and there are no *à priori* arguments or positive facts which would lead us to suppose that the activity of animal living substance cannot accomplish the latter as well as the former of these changes. We are quite ignorant it is true of the exact way in which either the hydration or the dehydration is effected by living substance; but we are equally ignorant of the exact way in which an amylolytic ferment effects the hydration of starch into sugar, which it carries out with so much apparent ease. It is not a great assumption to suppose that the continually changing living substance, which in its changes is continually giving out energy, has the power of acting on molecules of starch or of sugar in contact with, or even only near to itself, and so of hydrating starch into the sugar or of dehydrating sugar into starch. The latter process may be a more difficult one than the former, but not one beyond the power of the living substance. We may fairly suppose that a quantity of sugar in solution present in a vacuole, for instance, of the hepatic cell-substance can be, by some action of the cell-substance, converted into glycogen in a solid form, filling up the vacuole. Again, as we have incidentally mentioned, sugar injected into the jugular vein readily gives rise to sugar in the urine; but a very considerable quantity can be slowly injected into the portal vein without any appearing in the urine. This suggests the idea that the liver, so to speak, catches the sugar as it is passing through the hepatic capillaries and at once dehydrates it into glycogen.

Similar considerations may also be applied to the case mentioned above of the appearance of glycogen in the hepatic cells of winter (fasting) frogs. We have reason to think that sugar makes its appearance as a product of the metabolism of various tissues. The sugar thus arising finding its way into blood may be made use of at once elsewhere, converted speedily for instance into carbonic acid and so got rid of. But we can readily imagine that under certain circumstances, as for instance when the activities of the animal were lessened by a low temperature, it was not so made use of and remained in the blood. If so it would in the course of the circulation be carried to the liver, and might be at once taken up by the hepatic cells and converted into glycogen; and these might be so active that the blood was never at any time allowed to remain loaded with sugar to such an extent as to permit a loss through the urine.

§ **461**. Upon such a view, the carbohydrate taken as food would be converted into glycogen by the agency of the hepatic cell, without at any time becoming an integral part of the living substance of the cell. Such a view may be the true one; but it is open for us to look at the matter in another light. We may push still further the analogy between the glycogen of the hepatic cell and the material with which a secreting cell is loaded. In dealing with secretion we saw reasons for regarding such a body as mucin to be a product of the metabolism of the cell-substance of the mucous cell; and we may similarly regard glycogen. or sugar readily convertible into glycogen, or at least some or other carbohydrate material, as a normal product of the metabolism of the hepatic cell. We may thus conceive of the hepatic cells as being continually engaged in giving rise to carbohydrate material in the form either of sugar or of some other body; and we may suppose that under certain circumstances, as in the absence of adequate food, the carbohydrate material thus formed is at once discharged into the blood of the hepatic vein for the general use of the body, but that under other circumstances, as when an amylaceous meal has been taken, the immediate wants of the economy being covered by the carbohydrates of the meal, the carbohydrate products of the hepatic metabolism are stored up as glycogen. Under such a view the sugar of the meal is used up somewhere in the body, and the glycogen to the storage of which in the liver it gives rise comes direct from the hepatic substance. And a similar explanation may be given of the storing-up of glycogen in the liver under such circumstances as those of the winter frog previously mentioned.

We do not possess at present experimental or other evidence of so clear a kind as to enable us to decide dogmatically between these two views; we are limited to very general indications. We have seen that proteid food, though in this respect falling far below carbohydrate food, does or may give rise to a certain amount of glycogen in the liver; and gelatin seems to have the same effect. Further, in certain cases of the disease diabetes, of which we shall have to speak presently, and which is characterized by the presence of a large amount of sugar in the blood, sugar continues to be formed in large quantity, even when the diet is entirely restricted to proteid and fatty matters, all carbohydrates being excluded. Now in diabetes we have reason to believe that the large quantity of sugar in the blood is accompanied by a large deposition of glycogen in the liver, and indeed in other tissues; for in the few cases which have been examined sufficiently soon after death, and in which owing to the suddenness of the death, there was no opportunity for stored-up glycogen to disappear, a very large quantity of glycogen has been found in the liver or in some other organs. Hence the phenomena of diabetes may be taken as shewing, in a much more striking manner than do any experiments, that proteid material taken as food may give rise to hepatic glycogen. And this at first sight seems to afford proof that the hepatic glycogen is a product of the metabolism of the hepatic cell, the activity of the cell being stimulated as it were by the presence of the proteid food. But the proof is not cogent in the face of our ignorance of the metabolic changes which the proteid material of food undergoes in the body. As we shall insist upon in more detail later on, proteid material in giving rise to urea throws off somewhere in the body a large quantity of a carbon-containing radicle in some combination or other; the proteid contains far more carbon than is needed to unite with the nitrogen to form urea. We shall see that this excess of carbon has a tendency to appear in the form of fat, but we may readily suppose that it might temporarily as a preliminary process or under certain circumstances take on the form of sugar. And we may further suppose that the sugar is formed out of the proteid not in the liver but in some other tissue, in muscle for instance. But if so, hepatic glycogen which is the result of proteid food, may after all be formed in the liver by simple dehydration of sugar formed elsewhere, and brought to the liver in the portal blood.

We cannot, we say, at present decide between these two views; and indeed it may be that both views are true, or rather that the true conception embraces both views. It may be that the normal metabolism of the hepatic cell does produce a certain amount of carbohydrate material; but if so the probability is that the exact form in which that carbohydrate appears in the first instance in the laboratory of the cell is not that of glycogen but of sugar of some kind or other, and that the conversion into glycogen is a subsidiary act for the purpose of retaining the carbohydrate material in the grasp of the cell. If this be the case, then until it has been shewn that there is something peculiar about the sugar thus produced by the cell itself, by virtue of which it alone can be converted by the cell into glycogen, we may fairly infer that the cell might also convert into glycogen sugar passing into the interstices of the cell-substance from the portal capillaries.

§ **462**. We may now turn to another question, the answer of which is in a measure dependent on the one which we have just discussed. What is the use and purpose of this hepatic glycogen? What ultimately becomes of the glycogen thus for a while stored up in the liver?

One view which has been put forward is as follows. We have evidence, as we shall presently learn, that a great deal of the fat of the body is not taken as such in the food, but is constructed anew in the body out of other substances. Both carbohydrates and proteids, taken in excess or under certain circumstances, lead to an accumulation of fat; and we have reason to believe that carbohydrates on the one hand and the carbon-holding portions of various proteids on the other, may by some process or other be converted into fat. And it has been suggested that the glycogen in the liver is a phase of a constructive fatty metabolism, that it is material on its way to become fat.

The positive evidence in favour of this view is very scanty; it is almost limited to the facts that fat, sometimes in very large quantity, is found in the hepatic cells, that while fat itself taken as food leads to no increase in the hepatic glycogen, carbohydrates, which are especially fattening, are most active producers of glycogen, and that the fat present in the hepatic cells seems to be increased by such diets as naturally increase the glycogen in the liver. No evidence has been offered as to the occurrence in the hepatic cell of any of the several steps of the conversion of glycogen into fat, nor indeed has it been suggested what those steps are. The view indeed is almost exclusively based on the supposed proof that the blood of the hepatic vein contains during life no sugar, or at least not more than does the general blood or even the blood of the portal vein. From this it is inferred that the glycogen in the liver is not lost to the liver by becoming converted into sugar and so discharged into the hepatic blood, and therefore must be converted into some other substance, which substance is presumably fat. But this line of argument is one which cannnot safely be trusted. On the one hand it has been maintained both by older and more recent observers that the blood of the hepatic vein under normal conditions is richer in sugar than the blood of the portal vein or indeed of any other part of the vascular system; and this has been regarded as an indication that the liver is always engaged in discharging a certain quantity of sugar into the hepatic veins. On the other hand others maintain that the blood in the hepatic vein, if care be taken to keep the animal in a perfectly normal condition, contains no more sugar than does the blood of the right auricle or of the portal vein, and indeed that the liver itself, if examined before *any* post-mortem changes have had time to develope themselves, is absolutely free from sugar.

Normal hepatic blood may be obtained by means of an ingenious catheterisation. This consists in introducing through the jugular vein, into the superior, and so into the inferior vena cava, a long catheter, constructed in such a manner that the vena cava can at pleasure be plugged below the embouchement of the hepatic veins, and blood so drawn exclusively from the latter; or *vice versa.*

Now the quantitative determination of sugar in blood by any of the methods as yet suggested is open to many sources of error. And when the quantity of blood which is continually flowing through the liver is taken under consideration, it is obvious that an amount of sugar, which in the specimen of blood taken for examination fell within the limits of error of observation, might when multiplied by the whole quantity of blood, and by the number of times the blood passed through the liver in a certain time, reach dimensions quite sufficient to account for the conversion into sugar of the whole of the glycogen present in the liver at any given time. Hence we may safely conclude that the comparative analysis of hepatic and portal blood, if they do not of themselves prove that the liver is either continually or at intervals converting some of its glycogen into sugar and discharging this sugar into the general system, are at least not sufficiently trustworthy to disprove the possibility of such a discharge of sugar being one of the normal functions of the liver. Indeed it may be doubted whether any great trust can be laid on experiments of this kind. We may add that similar experiments have led one observer to deny wholly the connection between the sugar which may be found in the hepatic vein and the glycogen of the hepatic cells.

Refusing then to admit the validity of these experiments we may regard the view that glycogen is simply a stage in the formation of fat as not proved; and indeed we shall presently see reason to believe that fat is formed elsewhere.

Another view, one which has already been suggested while we were dealing with the manner of formation of glycogen, makes use of the formation of fat for the purposes of analogy only. Seeing that adipose tissue serves as a storehouse of fat which is not wanted by the body at the moment but may be wanted presently, the question readily presents itself, May not the hepatic glycogen have an analogous function? May we not regard the presence of glycogen in the liver as in large measure due to the fact that it is deposited there simply as a store of carbohydrate material, being accumulated whenever amylaceous material is abundant in the alimentary canal, and being converted into sugar and so drawn upon by the body at large to meet the general demands for carbohydrate material during the intervals when food is not being taken? And we can accept this view without being able to say definitely what becomes of the sugar thus thrown into the hepatic blood. It was formerly believed that this sugar underwent an immediate and direct oxidation as it was circulating in the blood but we have already dwelt (§ 359) on the objections to such a view. It is sufficient for us at the present to admit that the sugar is made use of in some way or other.

Now, many considerations lead us to believe that a certain average composition is necessary for that great internal medium the blood, in order that the several tissues may thrive upon it to the best advantage, one element of that composition being a certain percentage of sugar. It would appear that some at least if not all of the tissues are continually drawing upon the blood for sugar, and that hence a certain supply must be kept up to meet this demand. On the other hand an excess of sugar in the blood itself would be injurious to the tissues. And as a matter of fact we find that the quantity of sugar in blood is small but constant; it remains about the same when food is being taken as in the intervals between meals. If sugar be injected into the jugular vein in too large quantities or too rapidly, a certain quantity appears in the urine, indicating an effort of the system to throw off the excess and so bring back the blood to its average condition. The maintenance of such a constant percentage of sugar would obviously be provided for or at least largely assisted by the liver acting as a structure where the sugar might at once and without much labour be packed away in the form of the less soluble glycogen, at those times when, as during an amylaceous meal, sugar is rapidly passing into the blood, and there is a danger of the blood becoming loaded with far more sugar than is needed for the time being; and it may be incidentally noted that a larger quantity of sugar may be injected into the portal than into the jugular vein without any reappearing in the urine, apparently because a large portion of it is in such a case retained in the liver as glycogen. At those times, on the other hand, when we may suppose that sugar ceases to pass into the blood from the alimentary canal, the average percentage in the blood is maintained by the glycogen previously stored up becoming reconverted into sugar, and being slowly discharged into the hepatic blood.

Moreover, this view, that the glycogen of the liver is a reserve fund of carbohydrate material, is strongly supported by the analogy of the migration of starch in the vegetable kingdom. We know that the starch of the leaves of a plant, whether itself having previously passed through a glucose stage or not, is normally converted into sugar, and carried down to the roots or other parts, where it frequently becomes once more changed back again into starch.

But in thus putting prominently forward the value of the hepatic glycogen as a storehouse of carbohydrate material, we must not forget that the whole of the store is not necessarily destined for other tissues than the liver; it may be made use of in part by the hepatic cell itself. The storing-up of glycogen is only one of the many functions of the hepatic cell. We shall presently bring forward evidence as to the occurrence in the hepatic cell of metabolic processes, in addition to those more directly concerned with the secretion of bile and the deposition of glycogen. It may be that part of the hepatic glycogen is in and by means of the hepatic cell under certain circumstances converted into fat; and this would explain the frequent abundance of fat in the hepatic cells. But it will be observed that this is a very different thing from maintaining that the glycogen is wholly destined to become fat. The position which we are expounding now is that the primary purpose of the glycogenic function is to provide a store of glycogen for the needs of the body; by virtue of this the liver holds the balance as it were between the carbohydrate supply and demand of all parts of the body, whatever be the purpose served by the carbohydrate in this or that tissue; and all we are adding is that some of that material it may destine for itself, and that the use which it may make of it is to manufacture fat.

§ **463**. Glycogen is found in other parts of the body than the liver, and a study of the facts relating to the presence of glycogen in other tissues will help us to a true conception of the purpose of the hepatic glycogen. Next to the liver, the skeletal muscles are perhaps the most conspicuous glycogen holders. So frequently is glycogen found in muscle that it may be regarded as an ordinary though not an invariable constituent of that tissue; indeed it may almost be considered as a constituent of all contractile tissues. The quantity varies very largely both in the different muscles of the same animal and corresponding muscles of different animals. It disappears, according to some observers, readily upon starvation, even before the hepatic glycogen is exhausted; but all observers are not agreed on this point, and in some muscles, at least, it appears to be retained for a very long time. It is said to be increased in quantity when the nerve of the muscle is divided, and the muscle thus brought into a state of quiescence. On the other hand it diminishes or even disappears, being apparently converted into dextrose, when the muscle enters into rigor mortis. Some observers have found that it diminishes during tetanus, and maintain that it, after conversion into dextrose, is used up in the act of contraction, forming through its oxidation the immediate supply of the energy set free in the contraction. But even granting that the glycogen in a muscle may be diminished during prolonged labour, it cannot be admitted that the oxidation or other chemical change of glycogen is a necessary part of the ordinary metabolism of a muscular contraction, since many muscles wholly free from glycogen are perfectly well able to carry on long-continued contractions.

Another view of the use of glycogen in muscle is suggested by the fact that undeveloped embryonic muscles are peculiarly rich in glycogen. In a young embryo, at the time when the muscular substance, though undergoing striation, is still largely 'protoplasmic' in nature, the quantity of glycogen present is enormous; it frequently amounts to 40 p.c. of the dry material. At this period the hepatic cells are immature and very little glycogen is present in them. Later on, as the muscles become more wholly striated, the glycogen largely disappears from the muscle, and very soon afterwards begins to be stored up in the liver.

The meaning of this can hardly be mistaken. The glycogen in the immature muscle is a store of carbohydrate material, laid down on the spot, and ready at once to be used in what we may probably call the fierce metabolic struggle by which the simple protoplasmic cell-substance of the rudiment of the muscular fibre is transformed into the highly differentiated striated contractile substance. And we shall probably not err in considering the glycogen of the mature muscle to hold a similar position; it is carbohydrate material stored up on the spot, a local branch so to speak of the great carbohydrate bank. It is destined to become part of the contractile substance, and as such will contribute to the energy set free in a muscular contraction; but its energy is only available in this way after it has undergone the necessary metabolism and become part of muscular substance; it cannot be fired off in a contraction while it lies as raw glycogen, or even as dextrose, in the interstices of the muscular fibre. We have already (§ 87) discussed in part the metabolism of "contractile substance," and shall probably again return to it later on.

§ **464**. Glycogen may also be found in considerable quantity in the placenta. Here, as we shall see in a later part of this work, it is laid down in epithelial cells which lie on the boundary between the maternal and the fœtal tissues. And here too there can be little doubt that it is a store of carbohydrate material for the nourishment of the fœtus.

It has also been found in leucocytes, in cartilage corpuscles, especially in those large rapidly growing and rapidly multiplying cartilage corpuscles which lie in the outer zone of endochondral ossification, and in other situations. In cases of diabetes, where the body is overloaded with carbohydrate material, it has been found in considerable quantity in the testis, in the brain and elsewhere. Its occurrence in these situations, and under these circumstances, may be regarded as additional evidence of the truth of the view which we have expounded above that the main purpose of the deposition of glycogen is to afford a store, either general or local, of carbohydrate material, which can be packed away without much trouble so long as it remains glycogen, but which can be drawn upon as a source of soluble circulating sugar whenever the needs of this or that tissue demand it. It thus forms a very complete analogue to the vegetable starch, and fitly earns the name of animal starch.

We have some reasons for thinking that there are several varieties of glycogen, and that the glycogen which exists in muscle is not quite identical with that which occurs in the liver. Indeed there seem to be intermediate stages between glycogen and starch or dextrin. The physiological value of these differences has not yet however been clearly determined, and, with this caution, we may continue to speak of glycogen as a single substance.

Diabetes.

§ **465**. Natural diabetes is a disease characterized by the appearance of a large quantity of sugar in the urine, due, as we have already said, to the presence of an abnormal quantity of sugar in the blood. Into the pathology of the various forms of this disease it is impossible to enter here; but a temporary diabetes, the appearance for a while of a large quantity of sugar in the urine, may be artificially produced in animals in several ways.

If the medulla oblongata of a well-fed rabbit be punctured in the region which we have previously described (§ 176) as that of the vaso-motor centre (the area marked out as the "diabetic area" agreeing very closely with that defined as the vaso-motor area), though the animal need not necessarily be in any other way obviously affected by the operation, its urine will be found, in an hour or two, or even less, to be increased in amount and to contain a considerable quantity of sugar. A little later the quantity of sugar will have reached a maximum, after which it declines, and in a day or two, or even less, the urine will be again perfectly normal. The better fed the animal, or, more exactly, the richer in glycogen the liver, at the time of the operation, the greater the amount of sugar. If the animal be previously starved so that the liver contains little or no glycogen, the urine will after the operation contain little or no sugar. It is clear that the urinary sugar of this form of artificial diabetes comes from the glycogen of the liver. The puncture of the medulla causes such a change in the liver that the previously stored-up glycogen disappears, and the blood becomes loaded with sugar, much if not all of which passes away by the urine. In the absence of any proof to the contrary, we may assume that in this form of artificial diabetes the glycogen previously present in the liver becomes converted into sugar, just as we know that it does become so converted by post-mortem changes. The glycogenic function of the liver is therefore subject to the influence of the nervous system, and in particular to the influence of a region of the cerebro-spinal centre which we already know as the vaso-motor centre, or at least of a part of that region.

Before we attempt to discuss this nervous influence we must say a few words on the nerves of the liver.

§ **466**. The liver is supplied with nerves from the *hepatic* plexus, which passes into the liver at the porta and running in the portal canal with the hepatic artery and portal vein, is distributed to various parts of the organ. This plexus, which is the only nerve supply to the liver, consists partly of medullated and partly of non-medullated fibres, and is an extension of the great solar plexus already often mentioned. Into that plexus as we have already seen the right (posterior) vagus sends the greater part of its fibres, and in that plexus both the abdominal splanchnic nerves, major and minor, end, on both sides of the body. The left (anterior) vagus forms slight connections only with the solar plexus but sends off a very distinct branch directly to the hepatic plexus. The liver therefore has nervous connection with the central nervous system by both vagus nerves and by the (abdominal) splanchnic nerves. Besides this other nerve-fibres find their way through the splanchnic sympathetic chain, or possibly otherwise, to the solar plexus from the spinal cord without taking part in either of the splanchnic nerves; and these may perhaps join the hepatic plexus.

Concerning the destination of the fibres of the hepatic plexus within the liver we know little or nothing definitely. Some undoubtedly supply the hepatic artery and its branches; but we cannot at present say what proportion of the whole number of fibres end in this way. Some again are destined for the bile ducts, and before the plexus passes into the liver it sends fibres to the gall-bladder; these probably end in the muscular coats of these organs. Whether any of the nerve-fibres end in the remarkably muscular coats of the portal vein, or whether, as theoretical reasons would perhaps lead us to suppose, some are connected with the hepatic cells we do not for certain know, though some observers have claimed to have traced nerve-fibres directly into the hepatic cells.

§ **467**. With regard to the exact nature of the influence started by the puncture of the medulla, and the path by which that influence reaches the liver, our information is at present very imperfect. One thing seems clear, viz. that the influence in question is not carried down by the main vagus trunks; for not only has the section of both these nerves in the neck no marked effect in the way of producing diabetes; but the 'diabetic puncture' of the medulla oblongata is as efficient after division of both vagus nerves as before. Seeing how close to or almost identical with the vaso-motor centre is the diabetic centre if we may use the phrase, it seems natural to suppose that the undue conversion of glycogen into sugar which follows the puncture is the result of some vaso-motor disturbance in the liver, for instance dilation of the hepatic artery. But we have no clear proof that this is the true explanation, and indeed if the phenomena are the result of the failure of normal vaso-constrictor impulses, those impulses do not reach the liver by the tract which we should suppose them naturally to take, viz. from the vaso-constrictor region of the cord through the splanchnic nerves, for division of the splanchnic nerves even on both sides does not cause diabetes. Moreover that the effects are not due to vaso-dilator results is shewn by the fact that strychnia poisoning produces diabetes in frogs, and produces it by rapidly hurrying into sugar the hepatic store of glycogen. Now in strychnia poisoning the blood vessels are constricted, not dilated, their muscular fibres like the skeletal muscles being thrown into contraction by the action of the poison.

The vascular relations of the liver are it is true peculiar, the small hepatic artery contrasting with the wide portal vein; and it may be that the diabetic effects are contingent not so much on the absolute account of constriction or dilation of the hepatic artery, as on the relation of the flow through that artery to the flow through the portal vein. Indeed in support of this view may be adduced the statement that section of both splanchnic nerves not only does not cause diabetes but prevents the usual effects of the diabetic puncture; and this has been interpreted as shewing that the increased portal flow thus induced counterbalances the effects of dilation of the hepatic artery. But we have at present no exact information, and there is as yet nothing distinctly to negative the view that in this artificial diabetes the nervous influence is brought to bear on the hepatic cell itself.

There are some facts which seem to shew that the path of this nervous influence on its way to the liver from the spinal cord passes through the first thoracic ganglion, ganglion stellatum; but how it reaches the hepatic plexus from this ganglion is wholly unknown.

§ **468**. A temporary diabetes may be brought about by the administration of the substance phloridzin. This however is a glucoside, and part of the sugar which appears in the urine, after a dose of it, may come direct from the drug itself; but the quantity of sugar discharged is too great to be accounted for in this way, and similar diabetic effects are produced by the administration of phloretin, a derivate of phloridzin, not a glucoside, and not giving rise to sugar by its own decomposition. The sugar which appears in the urine after a dose of this substance seems to come in part at least from the hepatic store of glycogen when that is present; but the drug will give rise to sugar in the urine of starving animals, from whose livers (and other tissues) glycogen is presumably absent. In such cases the drug appears, in some way or other, to either stir up the hepatic cells to a manufacture of sugar (and this fact is worth remembering in relation to the discussion which we lately entered into (§ 461) as to the nature of the formation of glycogen) or to produce sugar out of some of the other tissues of the body.

Artificial diabetes is also a prominent symptom of urari poisoning. This is not due to the artificial respiration, which is had recourse to in order to keep the urarised animals alive; because, though disturbance of the respiratory functions sufficient to interfere with the hepatic circulation may produce sugar in the urine, artificial respiration may with care be carried on without any sugar making its appearance. Moreover, urari causes diabetes in frogs, although in these animals respiration can be satisfactorily carried on without any pulmonary respiratory movements. The exact way in which this form of diabetes is brought about has not yet been clearly made out.

A very similar diabetes is seen in carbonic oxide poisoning; and is one of the results of a sufficient dose of morphia, of amyl-nitrite and of some other drugs.

There can be no doubt that in diabetes, arising from whatever cause, the sugar appears in the urine because the blood contains more sugar than usual. The system can only dispose (either by oxidation, or as seems more probable in other ways) of a certain quantity of sugar in a certain time. Sugar injected into the jugular vein reappears in the urine whenever the injection becomes so rapid that the percentage of sugar in the blood reaches a certain (low) limit. Sugar in the urine means an excess of sugar in the blood. How in natural diabetes that excess arises has not at present been clearly made out. It may be that some forms of diabetes resemble the artificial diabetes just described as resulting from puncture of the medulla, and arise from a too rapid conversion of the hepatic glycogen, or from carbohydrate material failing to be stored up as glycogen, or from an excessive manufacture of carbohydrate material by the hepatic cells. All forms of diabetes however cannot be satisfactorily explained in this way; and it has been suggested, though adequate proof has not yet been supplied, that the sugar of diabetes is of a peculiar nature and accumulates in the blood because it is unable to undergo those changes, whatever they be, which befall the normal sugar of the blood. We cannot here discuss the subject in detail; but there is much to be said in favour of the view that the sources of the excess of sugar in the blood may be various, and hence that several distinct varieties of diabetes may exist. In severe cases of diabetes the aberrant nature of the metabolism which is going on in some or other of the tissues of the body is shewn by the appearance of abnormal substances in the urine. Thus acetone is frequently present, and the fatal issue of certain cases has been attributed to poisoning by that substance; oxybutyric acid and other various organic, chiefly volatile, acids are also sometimes present. But in respect to these and other abnormal bodies we are not at present clear whether they are like the sugar itself the products of an abnormal metabolism which is the root of the disease, or whether they are secondary products, that is to say, products of the general disordered metabolism induced by the constant presence in the blood of an excess of sugar. We have already in discussing the formation of glycogen called attention to the fact that in severe cases of diabetes the sugar must have a non-amylaceous source; and the fact that the urea is increased (and that too in some cases in ratio with the sugar) in diabetes, suggests that the sugar may arise from proteids which have been split up into a nitrogenous (urea) and a non-nitrogenous moiety, and so points out the way in which proteids may be a source of glycogen.

As a sort of converse to diabetes we may mention that the administration of arsenic in sufficient doses or for an adequate time prevents an accumulation of glycogen in the liver and apparently in the body generally, whatever be the diet used. The presence of the metal in the hepatic cell seems to prevent the cell-substance from manufacturing glycogen either from carbohydrate material brought to it, or out of its own substance. As another kind of converse we may also state that the administration of glycerine, especially through the alimentary canal, diminishes the effect of the diabetic puncture, or of morphia or other poisoning, in hurrying on the hepatic store of glycogen into sugar, and thus diminishes the sugar in the urine; the presence of the glycerine in the hepatic cell appears to be in some way a hindrance to the conversion of the glycogen into sugar. Now glycerine injected into the alimentary canal of a normal animal leads to an increase of glycogen in the liver; and the view very naturally suggests itself that this increase arising from the glycerine is to be explained by the glycerine inhibiting in some way a normal conversion of the glycogen store into sugar which is continually going on, and thus increasing for the time that store.

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SEC. 3. THE SPLEEN.

§ **469**. *The Structure of the Spleen.* We may now take up the consideration of the formation of the constituents of bile, a matter which in dealing with the secretion of bile (§ 256) we postponed. Of these constituents the most important are the "bile salts" on the one hand, and the bile pigment on the other. We will take the latter first; but since, as we have already said (§ 26) the bile pigment, bilirubin, appears to be derived from hæmoglobin, and since the spleen seems to be especially concerned in the changes which hæmoglobin undergoes in the body, we must first turn to the structure of that organ.

When a fresh spleen is cut across, the whole interior within the well-defined coat or *capsule* presents the appearance of a dark red spongy mass, traversed by irregularly disposed paler bands or *trabeculæ*, and mottled by the presence of white bodies about the size of a pin's head, *the Malpighian corpuscles*, also irregularly disposed. The whole organ is very soft, and, by squeezing or otherwise, small portions of the red spongy mass can be isolated in a semi-fluid pulpy condition, known as *spleen-pulp*. The redness is obviously due to red blood corpuscles; and it is clear, at the outset, that the spleen possesses an unusually large supply of blood, which moreover seems to be disposed in an unusual manner.

When by a stream of normal saline solution driven through its vessels as much blood as is possible is washed away from the spleen, and the organ is subsequently hardened in the usual way, preferably in a distended condition, sections reveal the following features. The capsule consists of an outer layer of connective tissue covered with epithelioid plates, forming the peritoneal coat, and continuous with this an inner deeper layer, composed of connective tissue with networks of elastic fibres and containing a certain number of bundles of plain muscular tissue; this deeper layer of the capsule gives off rounded or flattened bundles of the same nature as itself, which pass in all directions into the interior of the organ, branching and anastomosing freely; these are best developed towards the side or hilus, where the branches of the splenic artery with the splenic nerves enter, and whence the splenic veins issue. The mode of branching is irregular, and the branches vary in size, larger trabeculæ giving rise to smaller ones, so that the whole interior of the organ is divided into a labyrinth of irregular communicating chambers, which contain in the fresh state the spleen-pulp mentioned above.

The basis of both capsule and trabeculæ, small and great, is connective tissue well furnished with elastic elements. In some animals, as for instance in the dog, this basis is so richly provided with plain muscular fibres, that both trabeculæ and capsule (in its deeper layers) seem to be almost entirely composed of muscular tissue. In other animals, in man for instance, the muscular elements are much more scanty. The capsule and trabeculæ, small and great, thus form a sponge-like framework, which being elastic can, even in the cases where the muscular fibres are scanty or absent, at one moment be distended so that the chambers are capacious, and at another moment can by virtue of its elasticity shrink so that the chambers are reduced in size. In the animals in which muscular fibres are abundant still greater variations of size are possible. When the muscles are relaxed, a distending force, such as is furnished by the pressure of the blood-stream, can swell out the framework to a very great bulk; and an adequate contraction of the muscular fibres can in turn squeeze the sponge-like mass into very small dimensions. As we shall presently see, rhythmical or other contractions of the capsule and trabecular labyrinth, in animals in which these are largely muscular, do produce remarkable and important variations in the volume of the spleen.

§ **470**. This sponge-like framework of capsule and trabeculæ reminds one of the structure of a lymphatic gland, and the resemblance is carried still further by the chambers of the labyrinth being occupied by a reticular modification of connective tissue. But the resemblance is superficial only. The chambers marked out by the trabeculæ of the spleen are wholly irregular; there is not, as in a lymphatic gland, any distinction between a cortex with large radiating chambers and a medulla with anastomosing tubular chambers; the trabeculæ are closest towards the hilus, but otherwise one part of the spleen, as regards the arrangement of trabeculæ, is like any other. Moreover the reticular tissue occupying the chambers shews no distinction between lymph-sinus and follicle, is not exactly like the fine reticulum of the one or the coarse reticulum of the other, but of a nature distinct from each, and has no special connection with lymphatics, but has peculiar relations to the minute blood vessels.

Except at the white spots occupied by the Malpighian corpuscles, of which we will speak presently, the splenic reticulum is somewhat coarse, coarser than ordinary adenoid tissue (§ 259), and over a large part of the spleen is made up of branched nucleated cells, the branches of which are membranous and flange-like rather than filamentous. These flanges of neighbouring cells join with each other, and thus form a labyrinthine network, the walls of the minute passages of which are formed not of fibres but of irregular sheets. In some parts of the spleen, however, these flange-like processes are replaced by fibres, and, the bodies and nuclei of the constituent cells being rare, the reticulum appears as a more ordinary reticulum of fine fibres.

The bars of this reticulum, whether flange-like or filamentous, are at the edges of the trabeculæ continuous with the substance of the trabeculæ; the smaller trabeculæ break up into the reticulum, and the larger trabeculæ are fringed with processes continuous with the bars of the reticulum. Thus the coarser network of the trabecular system is continuous with the finer network of the reticulum.

The reticulum of the lymphatic gland contained, it will be remembered, besides fluid, leucocytes, these being crowded in the follicle and more sparse in the lymph sinus. The splenic reticulum also contains leucocytes, but these are thrown into the background by the large number of red corpuscles with which the meshes of the reticulum are crowded. The reticulum in fact is filled with blood; and peculiar arrangements exist by which the blood gains access to the spaces of the reticulum. What we spoke of above as 'spleen pulp' expressed from the fresh spleen consists of fragments of the reticulum together with the red and white corpuscles occupying the meshes of that reticulum.

§ **471**. The splenic arteries entering the spleen at the hilus are in some animals at first supported by the trabeculæ, along which they run dividing as they go, but the branches at last leave the trabeculæ and plunge into the reticulum. In other animals the arteries run more independent of the trabeculæ. As they leave the trabeculæ, or towards their terminations, the small arteries are apt to divide into pencils of small twigs. In a similar manner the veins may be traced back along the trabeculæ, small and great, along which they are gathered up from smaller veins of the reticulum; but the veins do not run in the reticulum as distinct vessels to the same extent that the arteries do.

In the reticulum the minute arteries, according to most observers, are not continuous in the usual manner with veins by means of closed capillaries; but a peculiar arrangement is met with. The epithelioid plates forming the capillary wall, instead of being cemented together to form a continuous tubular sheath, are separate from each other, come asunder as it were, and thus allow the lumen of the capillary or rather of the minute artery to open out into the splenic reticulum; indeed the epithelioid plates no longer retain their simple spindle shape, but becoming branched and irregular are transformed into the cells of the reticulum. In this way the channel of the blood vessel becomes continuous with the labyrinth of the splenic reticulum; and by a converse process the same labyrinth is made continuous with the plexiform beginnings of small veins, the so-called venous sinuses, which end in the veins running along the trabeculæ.

Thus the blood flowing along the splenic artery escapes from the open ends of the minute arteries into the splenic reticulum, and is gathered up from the reticulum into the open mouths of minute veins. When the capsule and trabeculæ are in a relaxed condition a not inconsiderable portion of blood thus escapes into the reticulum and tarries in the meshes where it undergoes changes of which we shall presently speak: when the capsule and trabeculæ are contracted and shrunken, the blood flows in a more direct manner through the narrowed channels from the arteries into the veins.

§ **472**. The lymphatic vessels of the spleen are not very numerous. The capsule and the trabeculæ contain lymphatic plexuses opening into lymphatic trunks, which leave the hilus with the blood vessels. There is, however, a remarkable lymphatic development, in the form of a sheath of adenoid tissue, which accompanies the arteries for some distance as they leave the trabeculæ and with which the lymphatic vessels of the trabeculæ are connected. So long as the arteries are running along the trabeculæ this adenoid sheath is either absent or extremely scanty; but as the finer arterial branches plunge into the reticulum, it is so increased in bulk at intervals, and especially where an artery is dividing into two, as to form an oval or spherical mass visible to the naked eye, and conspicuous from its colour because the adenoid tissue, crowded as usual with leucocytes, appears white or colourless as compared with the dark red spleen pulp. These, in fact, are the Malpighian corpuscles spoken of above. Each Malpighian corpuscle is a more or less globular mass of adenoid tissue, crowded with leucocytes, developed in the adventitia of a minute artery running in the splenic reticulum. As a rule the development takes place on one side of the artery, so that the rounded Malpighian corpuscle seems to be sitting on the artery. Sometimes the development takes place more or less regularly on all sides of the artery, so that the artery appears to pierce and run through the rounded mass, which is then called not a Malpighian corpuscle but a "hyperplasic spot"; and not infrequently the artery divides in the middle of the mass.

The adenoid tissue, as elsewhere (§ 259), is composed of a fine reticulum crowded with leucocytes; the corpuscle in fact closely resembles a solitary gland of the intestine or a rounded mass of the follicular substance of a lymphatic gland. But it differs from these structures in not being surrounded by any distinct lymph-sinus; at the circumference the true adenoid tissue passes suddenly into the coarser splenic reticulum. The artery as it passes through the Malpighian corpuscle gives off to it fine branches which form a capillary network through the adenoid tissue, and at the circumference open out into the labyrinth of the splenic reticulum. These Malpighian corpuscles are so numerous that in a section of a fresh normal spleen the dark red ground of the splenic substance appears quite mottled by reason of the white dots. Hence no inconsiderable portion of the blood reaching the spleen finds its way into the meshes of the splenic reticulum after passing through, and, probably after acting upon, and being acted upon by, the adenoid tissue of a Malpighian corpuscle.

What is known as *sago-spleen* is so called because the Malpighian corpuscles become enlarged and transparent, in consequence of the leucocytes undergoing 'lardaceous' degeneration ; the same change may also affect the adenoid tissue of the small arteries and may even spread to the spleen-pulp.

§ **473**. The nerves of the spleen which pass into the organ at the hilus with the blood vessels are derived from the solar plexus. They consist chiefly of non-medullated fibres mingled with which are a few medullated fibres. Their terminations have not been as yet exactly made out, but while many presumably are distributed to the blood vessels there can be little doubt that some end in the capsule and trabeculæ, at least where these contain muscular tissue, and thus bring the contractions of these structures under the guidance of the central nervous system.

The centripetal course of the fibres of these splenic nerves has not yet been made out definitely; we may perhaps safely conclude that the majority are derived, like the fibres distributed to the neighbouring abdominal organs, from the dorsal spinal cord. That the vagus also contributes fibres is very probable.

§ **474**. When the so-called spleen pulp is examined under the microscope, it is found to consist, besides the branched cells and fibres constituting the reticulum, of cells which may be described as partly red corpuscles and partly white corpuscles or leucocytes. We spoke of the meshes of the reticulum as being filled with blood; but it is obvious that the corpuscles of the blood must move less readily through the labyrinth than does the fluid plasma, and that hence a concentration of the corpuscles as compared with the plasma must take place in the meshes. The contents of the meshes cannot, properly speaking, be called blood, but are rather aggregations of corpuscles with a relatively small quantity of fluid.

The white corpuscles or leucocytes are very various. Some are small, like the leucocytes of a lymphatic gland, the cell-substance being scanty relatively to the nucleus. Others are indistinguishable from the ordinary white corpuscles of the blood. Others again are large, twice as large as an ordinary white corpuscle or even larger than this, possess more than one nucleus, and contain in their cell-substance numerous refractive, pale yellow or colourless granules. Some of these larger forms, which like the others exhibit amœboid movements, and are often irregular in form, are characterized by the presence in their cell-substance of red corpuscles, sometimes in almost a natural condition, sometimes more or less irregular in shape with their red hæmoglobin changing into the browner hæmatin, and sometimes disintegrated into a mass of brown granules. The fluid or plasma in which these cells float also contains besides normal red corpuscles a certain number of red corpuscles in various stages of change, as well as pigment granules which appear to be derived from hæmoglobin. Obviously a certain number of red corpuscles do undergo change in the spleen, but whether the change is mainly effected in the cell-substance of the cells just mentioned, or takes place in the plasma, the products of disintegration being subsequently taken up, in amœboid fashion, by the cells in question is not as yet clear. Besides the above, in the spleen of young animals, nucleated cells with hæmoglobin holding cell-substance, hæmatoblasts (see § 27), have been described; these are said to appear also in the spleen of adults after very great loss of blood.

§ **475**. *The Movements of the Spleen.* As we have already stated, the volume of the spleen is subject to considerable variations.

After a meal the spleen increases in size, reaching its maximum about five hours after the taking of food; it remains swollen for some time, and then returns to its normal bulk. In certain diseases, such as in the pyrexia attendant on certain fevers or inflammations, and more especially in ague, a somewhat similar temporary enlargement takes place. In prolonged ague a permanent hypertrophy of the spleen, the so-called ague-cake, occurs.

The turgescence of the spleen seems to be due to a relaxation both of the small arteries and of the muscular tissue of the capsule and of the trabeculæ; to be, in fact, a vascular dilation accompanied by a local inhibition of the tonic contraction of the other plain muscular fibres entering into the structure of the organ, the latter, at all events in some animals, being probably the more important of the two. And the condition of the spleen, like that of other vascular areas, appears to be regulated by the central nervous system, the digestive turgescence being fairly comparable to the flushed condition of the pancreas and of the gastric membrane during their phases of activity.

The application of the plethysmographic method to the spleen, carried out in the way which we described in speaking of the kidney (§ 410), enables us to study more exactly the variations in volume which the organ undergoes.

A 'spleen curve' (Fig. 95) taken in the same way as a 'kidney curve' does not, in the dog at all events, shew variations in the volume of the spleen corresponding with the pulse waves. The kidney curve, as we have seen (§ 410), gives clear indications of each heart-beat, but the spleen curve shews, besides the larger waves of which we shall speak directly, only undulations due to the respiratory movements; and these, always very slight, are sometimes not visible. In other words, the spleen does not expand with the increase of blood-pressure occurring in the splenic arteries after each heart-beat; this may be due to the muscular coat resisting expansion. Moreover when the supply of blood to the spleen is wholly and suddenly cut off, as by clamping the aorta, the spleen curve sinks very slowly, shewing that the spleen is diminishing in volume not suddenly but very slowly. The pathway of the blood through the splenic reticulum is peculiar; and increase or decrease in the volume of the spleen means more or less blood held in the spleen pulp, not necessarily a greater or less flow of blood through the organ.

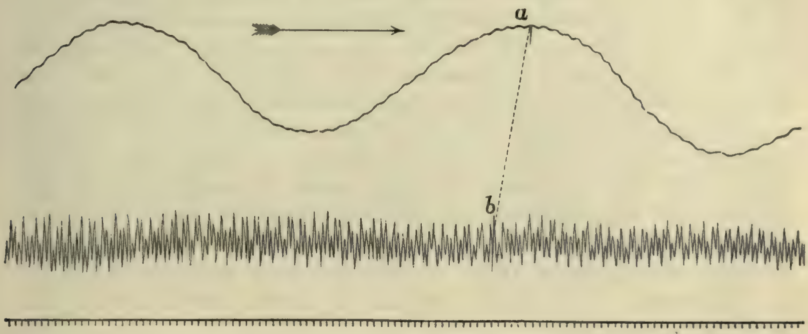

FIG. 95. NORMAL SPLEEN CURVE FROM DOG. (ROY.)

The upper curve is the spleen curve shewing the rhythmic contractions and expansions; the smaller waves are due to the respiratory movements. The lower curve is the blood-pressure curve, and the point *a* of the spleen curve corresponds in time to the point *b* of the blood-pressure curve. The marks on the time curve below indicate seconds.

Of special interest are the large slow variations of volume which, besides the respiratory undulations, the spleen curve usually shews, as seen in the figure. Rhythmic contractions and expansions, though not always present, frequently make their appearance, each contraction with its fellow expansion lasting in the cat and dog about a minute, and recurring with great regularity for a long time; and besides these the volume varies widely from time to time. There can be little doubt but that the rhythmic variations in volume are due in these animals to rhythmic contractions, with intervening relaxations, of the muscular trabeculæ and capsule; the slower variations are also probably due to the same cause. In many animals the contractility of the splenic tissue is shewn by the white lines of constriction which appear when the electrodes of an induction machine in action are drawn over its surface; and similar lines may be produced by mechanical stimulation with the point of a needle. So that the spleen in these animals may be considered as a muscular organ, now expanding to receive a larger quantity of blood and now contracting to drive the blood on to the liver. When the muscular elements are scanty in or absent from the capsule and trabeculæ, the expansion and contraction of the whole organ must depend alone or chiefly on variations in the width of the supplying arteries. We have evidence moreover that the muscular activity of the spleen, whether of the muscular capsule and trabeculæ and arteries combined or of the latter alone, is under the dominion of the nervous system. A rapid contraction of the spleen may be brought about in a direct manner by stimulation of the splanchnic or vagus nerves, or in a reflex manner by stimulation of the central end of a sensory nerve; it may also be caused by stimulation of the medulla oblongata with a galvanic current or by means of asphyxia. Though the matter has not yet been fully worked out, we have already sufficiently clear indications that the flow of blood through the spleen is, through the agency of the nervous system, varied to meet changing needs. At one time a small quantity of blood is passing through or is being held by the organ, and the metabolic changes which it undergoes in the transit are comparatively slight. At another time a larger quantity of blood enters the organ, and is let loose, so to speak, into the splenic pulp, there to undergo more profound changes, and afterwards to be ejected by the rhythmic contractions of the muscular trabeculæ.

It is further obvious that these changes going on in the spleen must have an important influence on the changes going on in the liver; it cannot be of indifference to the latter organ whether a relatively small quantity of blood, relatively little changed, reaches it from the spleen, or whether it receives a relatively large quantity of blood, profoundly altered by the changes which it has undergone in the spleen pulp.

§ **476**. *The Chemical Constituents of the Spleen.* Besides the chemical bodies which one would expect to find in a vascular, muscular organ full of blood, the spleen contains bodies, lodged apparently in the spleen pulp, which give it special chemical characters. One of the most important of these is a special proteid of the nature of alkali-albumin, holding iron in some way peculiarly associated with it. The occurrence of this ferruginous proteid, accompanied as it is by several peculiar but at present little understood pigments, rich in carbon, which are partly present in the cells spoken of above and partly deposited in the branched cells of the reticulum, appears to be connected with the changes undergone by the hæmoglobin which we shall presently discuss. The inorganic salts of the spleen, or at least those of its ash, are remarkable for the large amount of both soda and phosphates, and the small amount of potash and chlorides which they contain, thus differing from those of blood-corpuscles on the one hand, and from those of blood-serum on the other. But perhaps the most striking feature of the spleen-pulp is its richness in the so-called extractives. Of these the most common and plentiful are succinic, formic, acetic, butyric and lactic acids, inosit, leucin, xanthin, hypoxanthin and uric acid. Tyrosin apparently is not present in the perfectly fresh spleen, though leucin is: both are found when decomposition has set in. The constant presence of uric acid is remarkable, especially since it has been found even in the spleen of animals, such as the herbivora, whose urine contains none.

The richness of the spleen in these extractives is an indication of the importance of the metabolic events with which the organ has to do; but it will be more profitable to discuss what goes on in the spleen in connection with the metabolic changes in other parts of the body, in the liver for instance, than to attempt to lay down any so-called 'functions' of the spleen. When we confine our attention to the spleen itself we learn very little; thus the whole organ may be successfully removed without any very obvious changes in the economy resulting. We may return therefore to the discussion of the formation of the bilirubin of bile, and of the changes undergone by hæmoglobin, with which as we shall see the spleen is connected, and which moreover has to do with the formation of other pigments.

SEC. 4. THE FORMATION OF THE CONSTITUENTS OF BILE.

§ **477**. *Bile Pigments.* After extirpation of the liver no accumulation of bile pigment or bile salts takes place in the blood. This is well shewn in frogs, which survive the operation for some considerable time; but the same results have been obtained in birds (geese and ducks). There can be no doubt therefore that these substances are formed in the liver and not simply withdrawn from the blood by the liver in some such way as we have seen reason to think urea is withdrawn from the blood by the kidney.

When the plasma of circulating blood is made to contain hæmoglobin detached from the corpuscles, bile pigment frequently makes its appearance in the urine. The presence of free hæmoglobin may be obtained by injecting into the veins a solution of hæmoglobin or blood made 'laky' by freezing and thawing or by the addition of a small quantity of bile salts, or by simply injecting into the veins a quantity of distilled water or a small quantity of ether or chloroform or of bile salts, all of which tend to 'break up' red corpuscles and set free hæmoglobin. A similar result occurs in poisoning by certain drugs, such as toluylendiamine. Under these circumstances not only does bile pigment, bilirubin, make its appearance in the urine, but the quantity of bilirubin secreted by the liver is increased. Obviously the presence of dissolved hæmoglobin in the plasma of the blood, and, presumably more especially of the blood reaching the liver by the portal vein, leads to an increased formation of bilirubin, which takes place in such a manner that the whole of the bilirubin so formed does not pass into the bile but part is retained in or thrown back into the circulation and appears in the urine.

We have already mentioned the chemical connection between hæmoglobin and bilirubin. Hæmoglobin, after the detachment of its proteid component becomes hæmatin ($C_{32}H_{32}N_4FeO_4$). By treatment with sulphuric acid or otherwise (§ 351), hæmatin may be deprived of its iron; and this iron-free hæmatin (sometimes called hæmatoporphyrin) is said to have the composition $C_{32}H_{32}N_4O_5$, differing from bilirubin only in its oxygen and hydrogen ($C_{32}H_{32}N_4O_5 + 2H_2O - O = C_{32}H_{36}N_4O_6$)*. Moreover in old blood clots in the body the hæmoglobin of the clot becomes in time transformed into an iron-free body which has been called hæmatoidin, but which both in composition and in reactions appears to be identical with bilirubin.

These several facts lead us to the conclusion that the bilirubin of the bile is simply some of the hæmoglobin of the blood transformed by the throwing off of its proteid and its iron components. It is natural to suppose that the transformation takes place in and is effected by the agency of the hepatic cells; and this view is supported by the fact that the hepatic cells are characterized by containing certain peculiar iron compounds. When all the blood is carefully washed out of the liver by injection through the blood vessels, by which means the remaining bile is got rid of at the same time, the hepatic substance is found to contain a small quantity of iron, sufficient to give the cells a diffused dark colour when treated with ammonium sulphide; the exact amount appears to vary largely, but the causes of the variation have not been determined. That this iron is in organic combination is indicated by the fact that with potassium ferrocyanide and sulphocyanide the blue or red reaction is not observed until after treatment with hydrochloric acid. Apparently there are several such compounds, of a proteid or of a nuclein (§ 29) nature, from some of which the iron is more easily removed than others, and these compounds appear to be present in both the cell-substance and the nucleus. It will be remembered (§ 244) that bile contains a distinct quantity of iron, which probably has its origin in the iron thus set free from hæmoglobin and retained in the hepatic cell; but it does not follow that all the iron thus set free makes its way into the bile; and indeed the quantity of iron discharged in the bile in 24 hours is much smaller than the quantity calculated to be set free in the formation out of hæmoglobin of the quantity of bilirubin discharged during the same period. Apparently the iron compounds of the hepatic cell have some other work than the simple discharge of iron into the bile.

The fact mentioned above, that the presence of free hæmoglobin in the blood leads not only to an increase of bilirubin in the bile, but also to its presence in the urine, offers some difficulties; for if the bilirubin be formed out of hæmoglobin by and in the hepatic cell, one would expect to find that the whole of it passed into the bile, and that it could not appear in the blood and so in the urine unless reabsorption from the bile passages, due to obstruction, took place; and there is no evidence of any sufficient obstruction occurring in these cases. Indeed the presence of bilirubin in the urine in these cases has been urged by some as an argument that bilirubin is formed in the blood or at least elsewhere than in the liver and is simply excreted by the liver. Not only however, as stated above, is there no accumulation of bile in the blood after extirpation of the liver, but that operation prevents the appearance of bilirubin in the urine as a consequence of the presence of free hæmoglobin in the blood. The phenomena in question therefore do not disprove that the bilirubin is formed in the liver; they may be taken however to shew that that formation, viewed as a secretory act, is peculiar, since the hepatic cell appears under certain circumstances to discharge its product of secretion into the blood or lymph as well as into the bile passages.

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* Doubling the formula for bilirubin given in § 245.

§ **478**. We may assume then that the hepatic cell has the power of splitting up the hæmoglobin brought to it, and of discharging part as bilirubin while it retains for a time the iron component in some organic combination; and if we further assume that it works upon the entire hæmoglobin we may presume that it makes some subsequent use of the proteid component. But are we justified in assuming that the whole work is done by the hepatic cells? Are we to conclude that bilirubin is manufactured by some act of the hepatic cells which includes not only the conversion of hæmoglobin into bilirubin, but also the extraction of the hæmoglobin from the red corpuscles as these are streaming slowly through the lobular hepatic capillaries in close contact with the hepatic cells? Now, as far as we know at present, hæmoglobin can only be set free by means of a disintegration of the corpuscles; we have no instances of a corpuscle parting with some of its hæmoglobin and proceeding on its way otherwise unchanged; and we have no histological evidence of any disintegration of red corpuscles in the liver corresponding to the formation of bile. Nor can we draw any conclusion from the results of a comparative enumeration of red corpuscles in the portal and hepatic blood, for these are too insecure to rest any conclusion upon. On the other hand, as we have just seen, the presence in the plasma of the blood of hæmoglobin in a free condition is peculiarly potent in exciting the formation of bilirubin. The evidence therefore is very strong for the view that, as far as the formation of the greater part at least of the bilirubin is concerned, the action of the hepatic cell is limited to converting into bilirubin the free hæmoglobin offered to it by the portal blood.

By what means, under normal conditions, is the presence of that free hæmoglobin secured? We have seen reason (§ 474) to conclude from histological appearances that a certain number of red corpuscles undergo change in the spleen pulp; and it seems natural to infer that one duty of the spleen is to set free hæmoglobin from the corpuscles and thus, through the splenic veins and so the portal vein, to supply the liver with material for bilirubin. But this cannot be the only source, since the secretion of bile continues after extirpation of the spleen. There must therefore be other regions of the body in which a similar change of red corpuscles is going on; it has been suggested that the red marrow of bones is one of these; but further information on these points is needed.

Assuming that under normal circumstances the chief supply of material for the manufacture of bilirubin comes from the spleen, the question arises, Does that material leave the spleen in the form of hæmoglobin, or does the spleen still further assist in the matter, by effecting some preliminary change in the hæmoglobin, by converting it for instance into a proteid-less hæmatin-like body? And the same question may be also applied to the other tissues which may similarly provide material. Our knowledge is at present insufficient to furnish a satisfactory answer to such a question.

We may then go so far as to say that the bilirubin of the bile is derived from the hæmoglobin of the blood, and that the later stages of the transformation, including the discharge of the iron of the hæmatin component, take place in and by means of the hepatic cell; but much beyond this is at present uncertain. It must be remembered too that, though after extirpation of the liver no accumulation of bilirubin takes place, shewing that the bilirubin is formed by the liver and not elsewhere; yet the whole change from red corpuscle to bilirubin may occasionally take place quite apart from the liver, as shewn by the presence of hæmatoidin in old blood-clots.

§ **479**. *The formation of the bile-acids.* About this we know still less. Taking glycocholic and taurocholic acids as the typical bile acids, recognizing (§ 246) that these arise from the union of cholalic acid with glycin and taurin respectively, and remembering that taurin is found in several tissues, and that glycin (see § 419) though not an actual constituent of any of the tissues must certainly arise in tissue metabolism, we may conclude that the chief work in this respect of the hepatic cell is to provide the cholalic acid, and to effect the combination with glycin and taurin, though possibly some amount of either one or the other of these bodies may be furnished by the hepatic substance itself. As to how cholalic acid arises out of the metabolism of the hepatic cell we know no more than we do about the formation of kreatin in muscle or of pepsin in a gastric cell. We are equally ignorant about the origin of glycin and taurin, and cannot explain why in one animal glycocholic, and in another taurocholic acid is prominent in the bile, though the two bodies, as shewn especially by the presence of sulphur in the taurin, are widely different. It has been observed that the presence of bile in the intestine seems to excite the liver to increased biliary action; since the bile-acids are rapidly changed in the intestine and the cholalic acid speedily altered, it seems probable that the increased biliary activity is due to the absorption of the glycin and taurin respectively. From which we may conclude that the presence of these bodies stirs up the hepatic cell to an increased formation of cholalic acid.

§ **480**. As a general rule the formation of bile acids runs parallel with the formation of bile pigment, an increase or decrease of bile meaning an increase or decrease of both constituents. But there are some facts which seem to shew that the two actions may be dissociated. The condition or symptom known as 'jaundice' is essentially an excess of bilirubin in the blood, whereby the tissues such as the skin, and the fluids such as the urine are coloured with the yellow pigment. In most of the maladies of which jaundice is a symptom, there is evidence of an obstruction to the flow of bile through the bile passages; and the presence of bile in the blood and hence in the tissues at large is in such cases due to the fact that the bile after secretion by the hepatic cells is reabsorbed from the bile ducts, see § 256.

But in certain cases where jaundice is a prominent symptom, no evidence of any obstruction whatever to the flow of bile can be obtained. This is the case in the jaundice of yellow fever and of a peculiar allied malady known as 'acute yellow atrophy of the liver.' Now in these cases there is no evidence of an accumulation in the blood or elsewhere of bile-acids as there is of bile-pigment. And in the obscure malady known as simple or idiopathic jaundice, in which though the anatomical conditions are unknown there is at least no sign of obstruction, the urine though loaded with bile pigment is said to contain no bile acids.

It has been supposed that these cases afford proof that the bile may be formed elsewhere than in the liver. In face however of the arguments brought forward in the preceding paragraphs, they cannot be accepted as proof that the normal formation of bilirubin is so carried on; nor is there any evidence to shew that in these cases bilirubin is formed on a plan wholly different from the normal. And a different explanation seems possible. We may suppose that in these cases the metabolic activity of the hepatic cells is modified, and, further, so modified as while affecting largely the formation of bile salts and other functions of the hepatic cells, only partially to affect the formation and discharge of bilirubin, to affect indeed its discharge rather than its formation. That in acute yellow atrophy the functions of the cells are greatly affected is not only indicated by post mortem histological appearances, but is also shewn, as we shall presently have occasion to point out, by the substitution of leucin and tyrosin for urea in the urine. We have already commented on the fact that there is something peculiar in the action of the hepatic cell in secreting bilirubin inasmuch as the bilirubin so formed may, under certain circumstances, in part pass from the cell itself into the blood instead of into the bile passages. And we may perhaps explain the jaundice of the diseases under discussion by supposing that the morbid changes of the hepatic cells, while arresting the more difficult metabolic labours of the cells, such as the formation of bile-acids, do not put an end to the lighter task of turning haemoglobin into bilirubin, though so affecting that process also that the bilirubin passes into the blood instead of into the bile passages. In other words the formation of bilirubin is an act independent of and different from the more ordinary secretory activity of the cells.

§ **481.** The question may be asked, Is the secretion of bile independent of or in some way or other connected with the glycogenic activity of the cells? To this we cannot at present give a definite answer. In some of the invertebrata the cells in the organ, called a liver, which manufacture glycogen, are distinct from those which secrete bile or other digestive juices; and it might be inferred that in the vertebrate the two actions though taking place, as they certainly do, in the same cell, take place apart and distinct. There are facts which seem to indicate that the two are intimately connected; but we have as yet no exact knowledge concerning the matter. It has been urged that the portal blood is chiefly concerned with the formation of glycogen, and the blood of the hepatic artery with the secretion of bile; but there is no adequate support of this view. It must be remembered moreover that, in addition to the formation of glycogen and the secretion of bile, other metabolic events, especially affecting proteid or at least nitrogenous constituents of the body, are also taking place; and to these we must now turn.

SEC. 5. ON UREA AND ON NITROGENOUS METABOLISM IN GENERAL.

§ 482. We have seen that nitrogenous proteid material in some form or other enters into the composition of all the tissues of the body, and we have further seen that it is so conspicuously and constantly present wherever living substances are manifesting vital energies as to justify the conclusion that the changes which it undergoes are in some way essential to the manifestation of those energies. We have seen, it is true, reason to think that in some tissues at least, in muscle for instance, a large part of the energy set free during activity preexisted as latent energy and had its immediate source not in proteid (nitrogenous) but in some other constituents of muscle; and indeed, as we shall see later on, the greater part of the whole energy of the body must be regarded as the energy of carbon compounds and not of nitrogen compounds; but this is quite consistent with the view that proteid material in some way or other essentially intervenes in, we may perhaps go so far as to say directs, the changes by which in the body energy is set free in the peculiar way which we speak of as living.

We have seen that at all events the greater part of the proteid material of the food enters the blood as proteid material either as peptone or in some other form, and is carried as proteid material to the tissues.

We have seen that the nitrogen of proteid material leaves the body so largely in the form of urea, that the other nitrogenous excretions may for the time be left out of consideration.

And lastly we have seen reason to think that this urea which leaves the body in urine is brought to the kidneys as urea in the blood, the kidneys themselves apparently having no special power of forming urea out of something which is not urea, but only contributing to the general stock of urea by virtue of their own proteid metabolism. We have now to study the little we know concerning the steps by which the proteid material of the food and of the body is converted into this urea of the blood which is the source of the urea of the urine.

§ **483**. In the first place we may take it for granted that the urea carried to the kidney in the blood had an antecedent in something which was not urea. We can hardly suppose that the proteid constituent of living substance, when in the course of its metabolism it ceases to be proteid, breaks up at once into urea and into non-nitrogenous bodies. All we have learnt goes to shew that what we call metabolism is not a single abrupt change, but consists essentially in a series of changes; and we may safely conclude that proteid material in becoming urea passes through phases in which the nitrogen exists in chemical combinations distinct from proteid material on the one hand and urea on the other.

In the second place it is extremely probable that the series of changes by which proteid material becomes urea is not the same in all the tissues and on all occasions. We should naturally expect to find the proteid material following different lines of metabolism in different places or under different circumstances, the different lines all converging to the same body urea, because for some reasons or other urea appears to be, in the main, the most convenient form in which the nitrogen can leave the blood and the body.

We should accordingly expect to find, on the one hand, various nitrogenous bodies resulting from proteid metabolism in various parts of the body, and, on the other hand, arrangements by means of which these various bodies were reduced to the common form urea, preparatory to their discharge from the body by the kidney. And actual observation as far as it goes supports this view, though our knowledge of the whole matter is very imperfect.

§ **484**. We may turn our attention first to the metabolism of the skeletal muscles, since these represent, as far as mere quantity is concerned, by far the greater part of the proteid capital of the body. We may safely infer that they furnish a large part of the urea of the urine; though undoubtedly a small mass of tissue might by reason of its more rapid metabolism work over a greater quantity of proteid material than a much larger mass with a slower metabolism; yet we have no reason to think that the proteid metabolism of skeletal muscle, obscure though it is in its nature, is so slow as to neutralize the probable effect of the great bulk of muscle existing in the body.

In dealing with the chemistry of muscle (§ 62) we saw that urea, save in the exceptional instances of certain cartilaginous fishes, was conspicuous by its absence from the extract of muscle, whereas a very appreciable quantity of kreatin was invariably present, and indeed was the prominent nitrogenous crystalline constituent of that extract. It seems difficult to resist the conclusion that kreatin is the main normal nitrogenous product of the metabolism of skeletal muscles. If we accept this view, then upon the fact of the presence of kreatin in, and the absence of urea from, the muscle itself, we may base the conclusion that while the muscle produces kreatin as an antecedent of urea, the kreatin so produced is converted into urea in some part of the body other than the muscle itself. Kreatin as we have already seen may be easily split up, and we may probably with safety assume is split up somewhere in the body, into urea and sarcosin. But sarcosin does not appear in the urine as such; hence the conversion of kreatin into (part of) the urea of the urine entails as well the further conversion of sarcosin into urea. Now sarcosin as we have seen is methyl-glycin; we may regard it for our present purposes as simple glycin, and hence the total conversion of kreatin into urea entails the conversion of glycin into urea. This however does not offer any additional difficulty, since we know from direct observation that glycin introduced into the alimentary canal does not reappear as such in the urine but produces a corresponding increase in the urea of the urine; from which we infer that glycin absorbed from the alimentary canal is somewhere in the body converted into urea. We shall speak of this conversion later on, and shall then see that, as far as urea is concerned, glycin (amido-acetic acid) and sarcosin (methyl-glycin, methyl-amido-acetic acid) undergo the same change, the amide moiety in each case being converted into urea, while the non-nitrogenous moiety is oxidized and thrown off. Meanwhile we may state the conclusion at which we have provisionally arrived, namely that the nitrogenous metabolism of muscle probably gives rise to kreatin, which in some part of the body other than muscle is probably split up into urea, ready for excretion, and into sarcosin which also, somewhere in the body, is further converted into urea. And bearing in mind the large mass of the skeletal muscles, we may further conclude that a large portion of the urea leaving the body by the urine is formed in this way.

§ **485**. We must not however leave this statement without referring to a difficulty. Kreatinin as we have seen is so frequently found in urine as to be regarded as a normal constituent, at all events of human urine; and kreatinin is as we have seen the urinary form so to speak of kreatin; the one body easily changes into the other by the assumption or removal of H_2O. This suggests the question, Is not the kreatinin of urine the representative of the kreatin of the muscles, which is thus excreted directly without undergoing the change into urea just discussed? In answer to this we may say in the first place that the quantity of kreatinin in urine, though variable is small; we may put the average at about 1 grm. in 24 hours. Now muscle contains from ·2 to ·4 p.c. of kreatin; and this, taking the total muscle of the body (to say nothing of other sources of kreatin which we shall mention presently) at about 30 kilos would give 60 to 120 grms. kreatin as present in the muscles of the body at any one moment. We can hardly suppose that the metabolism of muscle is so slow as out of this stock only to provide the 1 grm.

of kreatinin in 24 hours. Moreover the kreatinin in urine vanishes during starvation, is very markedly increased by a diet of flesh which contains kreatin, and is not increased either by muscular exercise (which however would only indirectly affect the nitrogenous metabolism of muscle) or by such conditions, fever for instance, as notably increase the urea of urine by increasing the nitrogenous metabolism of muscle. We infer therefore that the normal presence of kreatinin in urine is due to the direct administration of kreatin present in a (normal) flesh diet and has nothing to do with the muscular metabolism of the individual who is secreting the kreatinin in his urine.

The fact however that the kreatin present in the muscle of the food and absorbed from the alimentary canal does not undergo a change into urea but is excreted as kreatinin, that is virtually as kreatin, warns us to be careful in adopting the conclusion arrived at above that the kreatin produced by muscular metabolism in the living body is a conspicuous antecedent of the urea of the urine. It is difficult to see why kreatin passing into the blood of the capillaries of the muscle should be changed into urea while that which passes into the capillaries of the portal system is not; for reasons which will be apparent presently we should rather expect that the latter being more directly exposed to the influence of the liver would be more readily and more completely converted than the former. Indeed the question forces itself upon us, Is kreatin after all the natural main product of the nitrogenous metabolism of muscle? Is it possible that in the normal metabolism of the living muscle the nitrogen leaves the muscular substance and passes into the blood in another form, as some substance not kreatin, and that it is as the muscle dies that kreatin is formed, just as the solid myosin is unknown to the living fibre but makes its appearance in a dying one? We have no positive evidence however that this is so, and meanwhile may continue to suppose that kreatin is formed, and that in consequence kreatin is a conspicuous antecedent of the urea of the urine; but we must not regard this as proved.

§ **486**. Our knowledge of the metabolism of the nervous tissues is, as we have seen, very imperfect (§ 72), but the presence of kreatin in the central nervous system leads us to infer that the nitrogenous metabolism of the living substance of nerve cells and of the axis cylinder of nerve fibres, is in its broad features identical with that of muscle substance. The mass however of the nerve cells and axis cylinders of the body, all put together, is small compared with the mass of skeletal muscle; moreover, the energy set free by the metabolism of a mass of nervous matter though 'higher' in quality is less in quantity than that set free by the metabolism of an equal mass of muscle, or in other words its metabolism is less rapid. Hence we may probably consider the metabolism of the nervous system as a mere addition to that of the muscular system, at least as regards the point on which we are now dwelling. The amount of nitrogenous metabolism taking place in connective tissue, cartilage, bone, and the skin is probably still less, and for our present purposes needs no special discussion.

§ **487**. The nitrogenous metabolism of the glands however, more particularly that of the liver, does deserve special consideration; and we may at once turn to a quite different aspect of the question in hand.

When the rate of discharge of urea from the body is observed during a period of some length, especially under varied circumstances, the direct effect of nitrogenous food becomes most striking. We have already said, and shall again return to the point, that muscular contraction does not directly increase the output of urea; the discharge of urea for instance is not necessarily increased by even great bodily labour. The introduction however of even a small quantity of proteid material into the alimentary canal at once increases the urea of the urine; and in the curve of the discharge of urea in the twenty-four hours each meal is followed by a conspicuous rise. The absorption of proteid material from the alimentary canal is followed by an immediate proportionate increase in the quantity of urea which is secreted by the kidneys, and that as we have seen means an increase in the urea brought to the kidney by the renal artery. What is the origin of this additional urea?

Two views present themselves. On the one hand since some portion of the proteid material of every meal, at all events of every necessary meal, goes to repair the proteid waste continually going on in the parts of the body where proteid metabolism is taking place, we may suppose that the presence of an extra quantity of proteid material thrown upon the blood from the food acts as a stimulus to the tissues, to the muscles for instance as well as others, stirs them up to increased nitrogenous metabolism and thus produces an increase of energy, chiefly if not exclusively in the form of heat, accompanied by an increase of the antecedents of urea and so of urea. In other words the increase of urea in question is the result of an increase in the general nitrogenous metabolism of the body.

On the other hand we may suppose that in order to prevent the whole body being encumbered with it, this excess of proteid food material is, in some special part of the body, split up into a nitrogenous and a non-nitrogenous moiety, and that, while the latter is stored up as fat or glycogen, the former is at once converted into urea and got rid of. We have already (§ 249) seen that a step in this direction may take place while the food is as yet in the alimentary canal; we have seen that pancreatic juice may carry part of the proteids on which it acts beyond the stage of albumose and peptone, and reduce that part into leucin, tyrosin, and other bodies. We do not know, as we have already said, to what extent this more profound digestion by pancreatic juice does actually take place in the living body; it may take place to a very slight extent and it may under certain circumstances take place to a considerable extent. But in any case it illustrates the way in which a somewhat similar disruption of proteid material, a disruption which may be broadly described as a splitting up of the proteid into a nitrogenous and a non-nitrogenous moiety, may take place somewhere in the body and so lead to the sudden formation of some antecedent of urea. The antecedent may be leucin or may be some other body or bodies.

In support of this view may be urged the fact that such bodies as leucin, glycin, asparagin and many others when introduced into the alimentary canal are transformed into urea. When these bodies are administered in not too great quantities they do not reappear in the urine but the urea is proportionately increased.

§ **488**. We have seen reason to think that the proteids of a meal are absorbed not by the lacteals but by the portal blood vessels, and such bodies as leucin probably take the same course. This being so, all these bodies pass through the liver and are subjected to such influences as may be exerted by the hepatic cells. Now we have no positive evidence that the liver does or can exert such an action on proteid material itself as to separate a relatively simple nitrogen compound from the remaining constituents, leaving these to form a body rich in carbon; we have no positive proof that the increase of proteid metabolism just spoken of as leading to an increase of urea takes place in the liver rather than in the tissues at large; we may go so far perhaps as to suspect that it is largely or wholly confined to the liver, but we have no convincing demonstration. We have however a convergence of evidence that the last stage of the process, namely the conversion into urea of some or other product of proteid metabolism which though allied to is not exactly urea does occur in the liver. In the first place, a large quantity of urea seems to be present in the liver of mammals; in this respect the liver presents a strong contrast to the muscles; in the liver of birds the urea is represented by urates. Moreover when a stream of fresh blood is passed several times through the liver of an animal recently killed, the percentage of urea in the blood so used is found to be decidedly increased. This however does not prove that urea is formed in the liver, since the increased quantity of urea in the blood which had been circulated might have been simply urea which had been washed out from the liver, where it had previously been staying, Still as far as it goes it is suggestive. In the second place, in certain cases of a form of disease of the liver known as acute yellow atrophy in which the hepatic cells are so changed that their functional activity is largely diminished, the urea of the urine not only undergoes a very marked decrease but appears to be replaced to a very large extent by leucin. This fact suggests that leucin (and not for instance kreatin) is the chief immediate product of the nitrogenous metabolism of the body, and that the leucin thus produced is in a normal state of things converted into urea by the liver. And in this connection it may be remarked that not only is leucin found in nearly all the tissues after death, especially in the glandular tissues, but also appears with striking readiness in almost all decompositions of proteids, and is moreover a product of decomposition of gelatiniferous substances. Without going however so far as to conclude that leucin is the chief antecedent of urea, we may take the above observation as indicating that the normal liver has, in some way or other, the power of converting leucin into urea. If this be so then we may also venture to suppose that when such bodies as leucin, glycin, &c., introduced into the alimentary canal appear in the urine as urea the transformation has taken place in the liver. The body tyrosin which so often accompanies leucin, belonging as it does to the aromatic series, stands on a different footing from leucin and the like.

§ **489**. The transformation however of leucin into urea raises a new point of view. Leucin, as we know, is amido-caproic acid; and, with our present chemical knowledge, we can conceive of no other way in which leucin can be converted into urea than by the complete reduction of the former to the ammonia condition (the caproic acid residue being either elaborated into a fat or oxidized into carbonic acid) and by a reconstruction of the latter out of the ammonia so formed. We have a somewhat parallel case in glycin, which is amido-acetic acid; here too a reconstruction of urea out of an ammonia phase must take place. Moreover when ammonium chloride is given to a dog a very large portion reappears as urea, *i.e.* there is an increase in the urea of the urine corresponding to a large portion of the nitrogen contained in the ammonium chloride. And in the case of other animals also, indeed of man himself, there is evidence that somewhere in the body ammonia may be converted into urea. Hence in all these cases where ammonia or ammonia compounds are changed into urea the last step at all events is one of synthesis; and this suggests the possibility that in the ordinary proteid metabolism also, the downward katabolic series of changes may finish off with a synthetic effort, the last stage of the former being the appearance of an ammonia compound which is subsequently reconstructed into urea.

This synthesis, like the transformation of leucin and other bodies, probably takes place in the liver; and in support of this view we have a certain amount of experimental evidence. Birds may be kept alive after total extirpation of the liver for a longer time than can mammals; and when in geese the liver is removed the uric acid (representing in these animals the urea of the mammal) is largely decreased, while the ammonia of the urine is largely increased. After the removal of the liver also, leucin, glycin, and other amides or amido-acids administered by the alimentary canal no longer increase the uric acid of the urine, as they do in the intact animal. In these animals, the synthesis of ammonia compounds into uric acid, which is parallel to the synthesis into urea occurring in the mammal, seems to take place in the liver, and we may infer is in some way or other effected by the hepatic cells.

As to the exact way in which ammonia either as such or in form of an amide or amido-acid changes into urea we have no certain knowledge. Ammonium carbonate, we know, is readily formed out of urea by simple hydration, and we may imagine that the living organism can carry out the reverse process and dehydrate ammonium carbonate into urea. There is, however, a certain amount of evidence that not ammonium carbonate but ammonium carbamate is the immediate antecedent of urea; and indeed, out of the body, by electrolysing a solution of ammonium carbamate with alternating currents, a certain amount of urea may be artificially produced. But this is a matter too obscure to be discussed here.

§ **490**. *Uric Acid.* This, like urea, is a normal constituent of human urine, and, like urea, has been found in the blood, in the liver and in the spleen; it is a conspicuous constituent of an extract of the latter organ. In some animals, such as birds and most reptiles, it takes the place of urea. In various diseases the quantity in the urine is increased; and at times, as in gout, uric acid accumulates in the blood, and a deposit of urates takes place in the tissues. Since by oxidation a molecule of uric acid can be split up into two molecules of urea, and a molecule of some carbon acid, uric acid is commonly spoken of as a less oxidised product of proteid metabolism than urea. But there is no evidence whatever to shew that the former is a necessary antecedent of the latter; on the contrary, all the facts known go to shew that the appearance of uric acid is the result of a metabolism slightly diverging from that leading to urea; indeed it is probable that the divergence occurs towards the end of the series of changes, for urea given by the mouth to birds appears in the urine as uric acid, and, conversely, uric acid given to mammals appears in the urine as urea. We have no evidence to prove that the cause of the divergence lies in an insufficient supply of oxygen to the organism at large; on the contrary, uric acid occurs in the rapidly breathing birds as well as in the more torpid reptiles. Nor can the fact that in the frog again urea replaces uric acid be explained by reference to that animal having so large a cutaneous in addition to its pulmonary respiration. The final causes of the divergence are to be sought rather in the fact that urea is the form adapted to a fluid, and uric acid to a more solid excrement. Nor is there in man or the mammal any satisfactory physiological or clinical evidence that an increase of uric acid is the result of deficient oxidation. The absolute amount of uric acid discharged by man and its proportion to the urea passed at the same time varies a good deal. There is no positive evidence that the quantity excreted is necessarily increased by nitrogeneous diet, unless some disorder supervenes; indeed it is asserted that both absolutely and relatively to the urea the quantity excreted is greater upon a mixed diet than upon a highly proteid one. Alkalis in the food seem undoubtedly to diminish it, and alcohol, at least in excess, to increase it.

So far from considering uric acid as a less oxidized antecedent of urea we ought perhaps rather to regard its appearance as a result of a synthesis in which urea or some allied body takes part. As we have said uric acid may be formed synthetically by heating together urea and glycin; and it has more recently been similarly prepared from various allied bodies. As to where or how such a synthesis is effected in the living body, we know little or nothing for certain, and can only make conjectures. The constant presence of uric acid in the spleen however, and the frequently noted connection between a rise and fall of uric acid in the urine and variations in the volume and therefore presumably in the activity of the spleen, suggest that the change may be brought about in this organ; but it must be remembered that in birds and reptiles the formation of uric acid seems to be effected in the same organs as that of urea and in an analogous manner; and the arguments which we have used concerning the formation of urea in the liver of mammals may be applied to the formation of uric acid in the livers of birds and reptiles. It is more probable therefore that in the mammal the turn to uric acid rather than urea is given in the liver, the spleen however possibly playing its part also in the matter.

§ **491**. Of the meaning of the appearance in the tissues of such bodies as xanthin, hypoxanthin, guanin and the like, and of the exact nature of the metabolism which gives rise to them or which they themselves undergo, we know little or nothing. The presence of these several bodies may be taken as illustrating the complex and varied nature of proteid metabolism to which we referred above. Urea is the chief end-product of proteid metabolism, but that end is probably reached in several ways; so that probably a very large number of nitrogenous chemical substances make a momentary appearance in the body. Some of these fail to become urea, and either without or after further change make their appearance in the urine. But we do not know whether their appearance is accidental, the result of imperfect chemical machinery; or whether they, though small in quantity, serve some special ends in the economy. Perhaps sometimes or with some of them it is the one case, at other times or with others it is the other case.

When proteid material undergoes outside the body, either by the action of trypsin or as the result of decomposition or under the influence of chemical agents, that change by which it is converted into leucin, the leucin, which appears in some considerable quantities, is accompanied by tyrosin, which appears in smaller quantities, as well as by other bodies. The almost constant appearance of tyrosin as a result of the decomposition of proteid material leads one, as we have previously said, to the conception that some representative of the aromatic series enters into the constitution of proteid substance; and it is possible that the hippuric acid of flesh-eating animals derives its benzoic acid constituent from this aromatic radicle of proteid matter. Tyrosin itself does not appear in the body as a normal product of proteid metabolism, and we are therefore led to infer that in proteid metabolism the aromatic radicle takes on some other form. Whether as in tyrosin the aromatic (phenyl) nucleus is associated with an ammonia representative or no, we do not know. But if it is then, since neither tyrosin nor any similar body is a constituent of normal urine, the ammonia constituent is somewhere dissociated from the phenyl one; and while the former contributes to the stock of urea, the latter is either discharged by the urine as hippuric acid, having as we have seen effected in the kidney a new association with the ammonia representative glycin, or leaves the body as one or other of the urinary phenyl compounds, or possibly may be oxidized somewhere into carbonic acid and water. Our knowledge on this point is limited, but we have ventured to refer to the point since it further illustrates the complexity of proteid metabolism.

§ **492**. In speaking of urea (§ 401) we alluded to its relations to the cyanogen compounds. Bearing in mind the peculiarly large amount of energy set free as heat during the isomeric transformation of many cyanogen compounds, as well as the large store of potential energy existing in cyanogen itself, the heat of combustion of which is very large, and contrasting these properties with those of ammonia and the ammonia compounds, we cannot help being tempted towards the view that in the actual living structure the nitrogen exists in the form of cyanogen compounds, and that in the passage to dead nitrogenous waste, during which energy is set free, the cyanogen compound changes to the amide or other ammonia representative. And there are several facts which lend support to such a view, such as the presence of sulphocyanates in saliva and urine, which we may look upon as a sort of leakage of cyanogen factors, the artificial production of kreatinin out of cyanamide and sarcosin, and other facts. But the matter, though it deserves to be borne in mind, is too obscure to be dwelt on here.

§ **493**. We may now briefly sum up the varied discussions which have occupied us in the present section.

Urea is the main end-product of proteid metabolism. Unlike hippuric acid and some other constituents of urine, urea is simply excreted by the kidneys, being brought to them in the blood, they apparently, beyond the simple act of excretion, doing no more than merely contributing to the stock of urea in so far as they are masses of proteid material undergoing proteid metabolism as part of their general life. What are the immediate antecedents of urea we do not clearly know; but it is probable that they are not one but several and indeed possibly many. We have reason to think that urea may be formed out of amides or amido-acids, or out of ammonia itself by a synthetic process; and we have indications that this synthesis is effected in the liver by the agency of the hepatic cells. But we do not know whether this synthesis bears only on particular nitrogen-holding substances of food or of the body, or whether it comes into play in the normal metabolism of proteid material. If the kreatin which is so conspicuous a constituent of muscular and nervous structures is a stage in the direct line to urea, then the synthesis would affect only the sarcosin which the kreatin in becoming urea sets free. But we have seen that it is by no means clear that kreatin is such a stage.

The evidence as far as it goes tends to shew that the metabolism of proteid is very complex and varied, that a large number of nitrogen-holding substances make a momentary appearance in the body, taking origin at this or that step in the downward stairs of katabolic metabolism and changing into something else at the next step, and that the presence in various parts of the body and even in the urine, in small quantities, of so many varied nitrogenous crystalline substances, forming a large part of what are known as extractives, has to do with this varied metabolism. Possibly the transformations by which nitrogen thus passes downwards take place to a certain extent in such organs as the liver and the spleen which are remarkably rich in these extractives. But the whole story of proteid metabolism consists at present mostly of guesses and of gaps.

SEC. 6. ON SOME STRUCTURES AND PROCESSES OF OBSCURE NATURE.

§ **494**. *The Thyroid Body.* Certain structures of obscure nature, but probably connected in some way or other with some of the metabolic processes in the body, are often spoken of under the undesirable name of 'ductless glands.' Such are the thyroid body or gland, the pituitary body, the thymus, and the suprarenal capsules. These differ from each other so essentially, that the only plea which can be urged in favour of considering them together is convenience and our ignorance of their respective functions.

The thyroid body is the one of the group most deserving to be called a gland, since it, like the lungs, arises as a two-lobed diverticulum from the ventral surface of the anterior part of the alimentary canal, and at first, like the lungs also, behaves as if it were about to become a double racemose gland. The connection with the throat however, which should have become a duct, is soon obliterated, and the two lobes, united with each other by an isthmus across the trachea, lose all traces of any branching ducts within them and become transformed into masses of isolated ductless alveoli bound together with connective tissue.

Hence, when a section is taken through a hardened and prepared lobe of an adult thyroid, what is seen is a limiting capsule of connective tissue sending into the interior numerous septa, which surround and separate from each other round or oval spaces, the sections of the isolated alveoli. These are of variable size, some being visible to the naked eye, and each is lined by a single layer of low columnar or cubical nucleated cells resting on a basement membrane, leaving a large cavity, which in fresh specimens is filled with a glairy fluid. The cells present no special characters.

The septa of connective tissue, fairly rich in elastic elements but remarkably free from adipose tissue, contain numerous blood vessels derived from the superior and inferior thyroid arteries, the branches of which, relatively large and frequently anastomosing, end for the most part in capillary networks round the alveoli; from these capillaries and those of the septa the blood is gathered into veins also relatively large, which forming plexuses on the surface of the organ end in the superior middle and inferior thyroid veins. The thyroid body is thus furnished with an abundant supply of blood.

The septa also contain a very large number of lymphatic vessels, which, both on the surface of the organ and along the septa, are arranged in plexuses of anastomosing trunks of considerable size. Small nodules of adenoid tissue are also found in the septa.

The nerves of the thyroid body are also abundant. They are, in man, derived chiefly from the cervical sympathetic nerve, passing off from the middle and lower cervical ganglia; their exact terminations within the organ is not known. Fine filaments are also said to be given off to it from the external branch of the superior laryngeal nerve.

The 'accessory' thyroid bodies often found are of the same nature as the main body.

Very frequently, so frequently in the adult as to be of almost normal occurrence, the alveoli contain not simple glairy fluid but a more solid clear material, called 'colloid'; this generally appears in the centre of an alveolus and may fill up the whole lumen; occasionally more or less changed epithelial cells may be seen lying between it and the layer of cells resting on the basement membrane. Extravasations of blood into the alveoli are also not uncommon.

The thyroid body is very apt to become enlarged, sometimes enormously so; and is then spoken of as *goitre*. The enlargement may be due simply to an increase in the number of otherwise fairly normal alveoli and septa. But very often a number of alveoli become more or less confluent, forming a cyst; and at times the whole gland appears to be composed of a number of cysts of varying size, frequently loaded with 'colloid' material. There is also a form of goitre in which the enlargement is chiefly or even exclusively due to an increase in the vascular supply, the blood vessels being abnormally distended; and this apparently may occur without any structural changes in the walls of the blood vessels. Sometimes however the arteries undergo aneurismal enlargements, with changes in their coats.

The glairiness of the fluid contents of the alveoli has generally been attributed to the presence of mucin, and this body has also been said to have been found within the lymphatic vessels running in the septa; but some observers have urged that the material in question is not true mucin, but a peculiar form (or forms) of proteid substance. The 'colloid' material so frequently appearing has also been regarded as allied to mucin, but its exact nature has not as yet been satisfactorily determined. Besides these special substances the alveoli or cysts also contain serum-albumin and globulin. The 'extractives' of the thyroid appear to contain kreatin or kreatinin in not inconsiderable quantities, xanthin, and lactic (paralactic) acid; guanin is said to be absent. In large and old cysts cholesterin is sometimes present; and when, as often happens, extravasations of blood into the cysts have taken place, haemoglobin, or at a later stage haematoidin (bilirubin), has been found.

§ **495**. The large supply of blood to the thyroid suggests the idea that the organ is the seat of some of the subsidiary metabolic processes to which we referred in the last section, and this view is supported by the presence of the extractives just mentioned; but we have no detailed knowledge of what actually goes on.

The presence of the peculiar mucin-like body in the alveoli, and the tendency to 'colloid' formation, further suggest some relation of the organ to the formation or distribution of mucin; and this view has derived a certain support from some experimental results, but these though numerous have proved neither uniform nor accordant. When in certain animals (monkeys, dogs and other carnivora, and the same has been observed in man) the gland is extirpated, even with the greatest care, the operation is frequently followed by the occurrence of peculiar nervous symptoms, such as muscular twitchings and tremors, spasms, and even tetanic convulsions (more especially observed in young animals), accompanied or succeeded by irregularity or failure of voluntary movements; subsequently there may ensue varied symptoms which may be described under the general term of disordered nutrition, ending eventually in death. In a certain number of cases however, in the above kinds of animal, no serious symptoms follow, even the total extirpation of the organ producing no marked effect; and in rabbits and other herbivorous animals removal is said never to be followed by any of the above results. It has been urged that the symptoms when seen are the effects not of the mere absence of the organ but of mischief set up by the operation in adjoining structures, more especially in the laryngeal nerves and vagus trunks; but this does not seem a valid explanation. If, as suggested above, certain metabolic processes are normally going on in the organ, we may fairly suppose that, in the absence of the organ, the interruption of the normal sequence of chemical change would throw upon the circulation certain strange substances which acting like a poison might produce the nervous symptoms, throw into disorder the nutrition of various tissues, and finally bring about death. We may further explain the cases where symptoms are absent by supposing that, for some reason or other "things have taken a different turn", the particular poisonous substances have not made their appearance but innocuous ones have taken their place; and we know how slight a change in chemical composition may turn a poison into an inert body. This of course remains a mere supposition until we can state what the exact metabolic processes are, and name the substances which work the mischief; but it seems more reasonable to accept such a provisional supposition than to conclude that the thyroid may be removed without producing any effect whatever on the organism. An animal without a thyroid may appear perfectly well because the circumstances to which it is exposed do not happen to test the imperfection from which it is really suffering, just as a man's inability to swim may not be apparent until he happen to fall into the water. The animals which do succumb to the operation of removal of the organ are, for some reason or other, put to the test, and are found wanting. The very discordance of the experimental results points the physiological moral that the phenomena which we are as yet able to observe form as it were a mere surface covering intricate processes at present wholly or nearly wholly hidden from us.

The above experimental results receive additional interest and at the same time support from clinical experience. The connection between goitre and cretinism, the latter disease being broadly speaking a result of disordered nutrition telling largely on the nervous system, has long been recognised; and attention has also been called to some tie between disease of the thyroid and a morbid condition, known as myxœdema, in a certain number of cases of which mucin or a mucin-like body has been found in great excess in the skin and in other tissues. In monkeys the removal of the thyroid has, in some cases, been followed, besides the symptoms mentioned above, some of which resemble those of myxœdema, by an accumulation of mucin or a mucin-like body in the skin and various tissues. It is very difficult not to connect this with the formation in the thyroid of colloid material in the contents of the alveoli. But we know so little about the nature of mucin and its allies, about their real relations to more ordinary proteid substances, and about the part which they play in physiological processes, that any views as to the exact connection between the presence of mucin in the tissues at large and changes taking place in the thyroid must be at present to a large extent speculation.

The large vascular supply of the thyroid, and the phenomena of a disease known as exophthalmic goitre, in which vascular enlargement of the thyroid is associated with cardiac symptoms and other vascular disturbances, especially of the head, have suggested that, apart from metabolic processes, the circulation in the thyroid may, perhaps in a more or less mechanical way, be connected with and influence the circulation in the brain. But the exact nature of this influence has not been made clear.

§ **496**. *The Pituitary Body.* The lower, posterior, lobe of this organ resembles the thyroid body (the upper, anterior, lobe is of quite distinct nature, being really a part of the central nervous system) in as much as it is a diverticulum of the alimentary canal (namely of the mouth), which instead of becoming a branched gland is converted into a mass of round, or oval, or cylindrical alveoli separated by septa of vascular connective tissue. Though in some instances the alveoli of the pituitary body like those of the thyroid possess a lumen, which moreover may hold more or less 'colloid' contents, the majority are solid masses of epithelial cells. The cells, which are columnar or polyhedral, present no special characters, except perhaps that between the usual epithelial cells are occasionally found spindle-shaped cells, apparently of mesoblastic origin.

Concerning the processes which take place in these alveoli and the purposes of the organ as a whole we know absolutely nothing.

§ **497**. *The Suprarenal Bodies*. A (mammalian) suprarenal body when cut across is seen to consist of two distinct parts, an outer thicker *cortical* part, of yellowish colour, striated radially, and an inner thinner *medullary* part of darker colour. At the depression on the anterior surface called the hilus, whence issues the comparatively large suprarenal vein, the cortex thins away so that the medulla comes to the surface. These two parts, cortex and medulla, are not, like the cortex and medulla of a lymphatic gland, different arrangements of the same material, but are of essentially different nature and indeed are of different origin. The medulla is derived from, is a modification of, sympathetic ganglia, while the cortex is derived from masses of mesoblastic cells surrounding the great blood vessels; and in some animals the two form wholly separate bodies. The so-called accessory suprarenals are composed of cortex alone.

The whole organ is surrounded by a capsule of connective tissue, free from muscular fibres and not very rich in elastic elements. From the capsule septa pass inwards and form a frame work, the cavities of which are filled by cells or groups of cells differing in nature and differently arranged in the cortex and in the medulla. The middle larger part of the cortex is composed of somewhat long solid columns of polyhedral cells, lodged in corresponding meshes of the frame work. The columns, which are three or four cells thick and several cells in length, though somewhat irregular and varying in size, do not anastomose, being wholly separated from each other by the bars of connective tissue, and possess no central cavity or lumen. The blood vessels which are abundant in these bars of connective tissue do not penetrate the columns. The cell-substance of the cells is of a yellowish colour, often containing yellowish oil globules, and possesses a clear round nucleus.

In the outer part of the cortex immediately underneath the capsule is a thin zone in which the groups of cells are not columnar but rounded and irregular; and again in the inner part of the cortex abutting on the medulla is another thin zone, in which the columnar arrangement is lost, the cells being here disposed in a network of thin cords and the individual cells to a large extent separated from each other by delicate continuations of the coarser connective tissue septa. Hence the main median part of the cortex, which from the prominent columnar arrangement appears striated radially, is often called the zona fasciculata, the thin outer part the zona glomerulosa, and the thin inner part the zona reticularis; but as far as the essential characters of the cells are concerned all the three zones are alike.

The medulla also consists of cells or groups of cells lying in the meshes of a connective tissue frame-work, but the cells are of a different nature from those of the cortex. They are irregular and often branched, and their cell-substance, though it sometimes contains pigment, is generally clear and transparent. The medulla moreover is further distinguished from the cortex by the abundant supply of blood vessels and of nerves.

The cells of the medulla and of the inner zone (zona reticularis) of the cortex are very apt to undergo change after death, and to become diffluent.

The arteries which come from the aorta and from the renal and phrenic arteries pass into the organ on the surface, and traversing the cortex, supplying as they go both capsule and cortex with a moderate number of vessels, end in the medulla, the connective tissue bars of which bear numerous large venous sinuses, into which the capillaries pour their blood, and from which the blood is gathered up into the suprarenal vein.

A large number of nerves, consisting chiefly of medullated fibres from the solar plexus, the renal plexus, the phrenic nerve and the vagus, pass into the suprarenal body at the hilus and on the under surface, and forming numerous plexuses coarse and fine, some carrying small groups of nerve cells, end chiefly in the medulla, though some pass on to the cortex. The ultimate endings are not yet known.

The lymphatics are fairly numerous and form plexuses in the capsule and in the connective tissue of the frame-work; it is stated that the lymphatic vessels surrounding the groups of cells in the cortex communicate with spaces between the cells.

§ **498**. Besides the ordinary proteid and other chemical constituents, the suprarenal body contains some substance or substances, possessing striking colour reactions, giving a dark blue or dark green colour with ferric chloride, and a carmine red tint with various oxidizing agents. This substance (whose nature is not exactly known, and which is confined to or most abundant in the medulla) is not soluble in the ordinary solvents of pigments, such as alcohol, ether, chloroform &c., but is readily soluble in dilute acids.

Among the extractives, hippuric, or benzoic acid, and taurocholic acid or taurin have been found, but it is not certain that these are normal constituents.

§ **499**. Some of the histological features of the suprarenal bodies, namely the groups of cells and their abundant blood supply, suggest on the one hand that important metabolic processes take place in them, some of which are probably connected with the history of the pigments of the body at large. On the other hand the unusually large nerve supply, and the derivation of part of the body from the sympathetic ganglia, suggest peculiar nervous connections. And the organ has often served as a starting point for speculations in these two directions; but our exact knowledge concerning them is very limited. The results of experiment have taught us little; extirpation for example has been often followed by the death of the animal operated upon, but the cause of the death in such cases is by no means clear.

One fact, gained by clinical experience, is the only real item of knowledge which we possess. Disease of the suprarenal bodies, apparently tubercular in nature and beginning in the medulla, is so often associated with a change in the colour of, with an increase of the pigment of the skin, 'bronzed skin', 'Addison's disease', that some connection between the two must exist; but the several links of the chain are as yet unknown. It is tempting to associate the increase of pigment in the bronzed skin with the chromogen or colour-yielding substance spoken of above; but we have no warrant for doing so, such for instance as any indication of ties between the suprarenal bodies and changes either in haemoglobin itself or in bilirubin, which two bodies we have reason to regard more particularly as mothers of pigment. Moreover the bronzed skin is only one of the symptoms of Addison's disease, failure of nutrition and nervous symptoms being also present.

§ 500. *The Thymus.* This, though it arises in the embryo as a paired outgrowth from the epithelial walls of a pair of visceral clefts, and thus begins as an epithelial structure into which mesoblastic elements subsequently intrude, soon puts on such characters as to appear essentially a lymphatic structure, and indeed might be regarded as a part of the lymphatic system.

It consists of a capsule of connective tissue, plain muscular fibres being absent, and septa or trabeculæ of the same nature which divide the organ into a number of irregular more or less cylindrical anastomosing follicles or lobules, and send finer radiating septa into the interior of each lobule. These lobules present the same characters throughout the whole mass of the organ, there not being, as in a lymphatic gland, any distinction between a cortex and a medulla of the whole body. The words are however applied to each lobule, to distinguish the central from the peripheral part of the lobule itself. Both the central medulla and the peripheral cortex of each lobule consist of a framework of reticular connective tissue, which in the cortex is identical with or closely allied to adenoid tissue, but in the medulla is coarser and more open and to a larger extent composed of branched anastomosing epithelioid cells. The meshes of the cortex are crowded with leucocytes, but these are much less abundant in and more easily fall out of the medulla, so that in sections the medulla appears more transparent than the cortex. It will be observed that this arrangement is almost the reverse of that obtaining in the alveolus of a lymphatic gland, in which the finer gland substance with its adenoid tissue crowded with leucocytes is placed in the centre, surrounded by the more open network of the lymph sinus.

The blood vessels of the thymus running along the septa form capillary networks which, though closer and more abundant in the cortical than in the medullary portions of the lobules, have no such special arrangement as obtains in lymphatic glands.

Lymphatic vessels, abundant in the capsule and septa, are undoubtedly in connection with the substance of the lobules.

The medullary substance frequently contains bodies, known as "concentric capsules", nests of concentrically disposed nucleated flattened epithelial or epithelioid cells. They appear to arise from a proliferation of the epithelioid cells lining small blood vessels, and have been supposed to be connected with the degenerative changes by which, with obliteration of the vessels, the whole organ dwindles away soon after birth.

§ **501**. From the thymus there may be extracted by means of saline solution a form of globulin or a proteid allied to globulin which, like the corresponding bodies from lymphatic glands or from leucocytes, seems to have some special relations to the formation of fibrin. Thus, as has already been said (§ 22), a solution of this globulin-like body from the thymus, injected into the veins, will give rise to extensive intravascular clotting.

The thymus, like the other bodies on which we are now dwelling, is also rich in extractives. Thus xanthin, hypoxanthin, leucin, lactic, succinic and other acids have been found in it.

But of what really takes place in the body we have no exact knowledge. Since the thymus is best developed before birth, disappearing after birth at a rate which varies much in different individuals and still more in different kinds of animals, and being eventually replaced by fat and connective tissue, it is obvious that its chief functions are in some way associated with events taking place before birth or in early life.

SEC. 7. THE HISTORY OF FAT. ADIPOSE TISSUE.

§ **502**. Globules of fat of various sizes make their appearance in the very elements of most of the tissues, in muscular fibres, in epithelial cells, in nerve cells, in leucocytes, and so on; and the medulla of medullated nerves consists largely of a peculiar fatty material. Besides this, certain cells of connective tissue at various times, and in various places, become so loaded with fat that groups of the cells become practically masses of fat. Connective tissue thus loaded with fat is called adipose tissue; and masses of adipose tissue of all manner of sizes and of shapes adapted to the several situations are found in various parts of the body. Many of the internal organs, more especially the kidneys, are wrapped in adipose tissue; but the largest deposit is one lying in the subcutaneous connective tissue, § 432, sometimes called the "panniculus adiposus"; and a 'fat' body is distinguished from a 'lean' body chiefly, though by no means exclusively, by the amount of subcutaneous adipose tissue.

Of all the tissues of the body adipose tissue is the most fluctuating in bulk; within a very short space of time a large amount of adipose tissue may disappear, and within an almost equally short time the quantity present in a body may be several times multiplied. When too much or too little food is given it is the subcutaneous adipose tissue which first and most rapidly increases or decreases in bulk.

§ **503**. A small piece of adipose tissue, examined under a low power, appears to be made up almost entirely of rounded masses of highly refractive material, closely packed together. These rounded masses, which stain an intense black with osmic acid and give other reactions of fat, are arranged in irregular lobules; between the lobules, and between the individual rounded masses, may be seen a small amount of fibrillated connective tissue carrying blood vessels.

When the tissue has been hardened and stained, and the fat has been removed by solvents, what was previously only visible as a rounded mass of fat is now seen, under higher powers, to be a cell, but a cell nearly the whole of the cell-substance of which has become transformed into a single large vacuole. Over the greater part of the circumference of the cell the cell-substance is reduced to a mere thin shell or envelope, or cell-membrane, but at one part a thicker disc-like remnant is seen, and in this is placed a rounded or oval, often flattened nucleus. Between these *fat-cells* may be seen a few bundles of connective tissue forming a scanty loose network, the rounded meshes of which are occupied by the fat-cells, the matrix of the bundles appearing at places continuous with, or adherent to, the envelopes of the cells; ordinary connective tissue corpuscles are also here and there present, though rarely visible between the larger, 50μ to 130μ, fat-cells. In injected specimens it is further seen that the connective tissue meshwork carries small blood vessels, which form capillary networks round the groups of fat-cells and even round individual cells. After death, upon cooling, the fat in the fat-cells may solidify in crystals.

It is obvious that a fat-cell is a cell, belonging to connective tissue, in the cell-substance of which fat has been collected to such an extent that the cell, which increases largely in bulk during the process, is almost wholly transformed into a large vacuole filled with fat, the cell-substance being reduced to a thin envelope of the vacuole, thickened at one part where the nucleus, thrust on one side by the gathering fat, is placed. Adipose tissue is a collection of such fat-cells held together by a meagre quantity of vascular connective tissue.

By studying the development of adipose tissue in the embryo or elsewhere, we may trace out the steps of the formation of the fat-cells. In the embryo, in a situation where adipose tissue is about to be formed, the connective tissue is seen to contain a number of small nucleated cells, rounded or somewhat irregular in form, the cell-substance of which at first presents no special characters, and contains not more than what may be called the ordinary amount of fat globules or spherules. Very soon however these minute drops or specks increase in number, the cell-substance at the same time increasing in bulk while remaining round or becoming more distinctly so, and the smaller drops run together into larger ones. This goes on; the fat increasing in quantity coalesces more and more, and the cell, as a whole, becomes larger and larger, the cell-substance at first keeping up in bulk with the increasing fat, but subsequently ceasing to increase, being apparently used up in the formation of the fat. Thus the original small 'protoplasmic' cell is at last transformed into the larger fat-cell, all the fat having run together into a vesicle the envelope of which, thickened on one side to carry the nucleus, is furnished by the remnant of the cell-substance. In some cases, the nucleus instead of being pushed early on one side, remains central though the collection of fat has become considerable; it is however eventually displaced. The whole process appears very similar to the deposition of mucin in the cells of a mucous gland, § 235; and we may by analogy infer that the fat-cell becomes a fat-cell by the cell manufacturing fat in some way or other, and depositing the fat so formed in the interstices of its substance. The most striking superficial distinctions seem to be that in the mucous cell the granules or spherules remain discrete within the cell, being separated by bars of cell substance, whereas in the fat-cell the globules, as they form, run together until at last they unite into a single mass; and further that while in the mucous cell, even when most heavily loaded, a relatively large amount of active cell-substance still remains, in the fat-cell a mere remnant is left and that chiefly surrounding the displaced nucleus.

Some observers are of opinion that the cells belonging to connective tissue which thus become fat-cells of adipose tissue belong exclusively to the kind which we spoke of as plasma cells, § 105; but this is doubtful. Others again, while admitting that the cells which become fat-cells resemble in appearance ordinary connective tissue corpuscles and may like them be branched, believe them nevertheless to constitute a special kind of connective tissue corpuscle, being led to this view by the fact, that though adipose tissue is very generally distributed throughout the connective tissue of the body, it is apt to appear in particular situations rather than in others, and in some tracts of connective tissue never under normal circumstances makes its appearance. Others again maintain that, under favourable circumstances, any connective corpuscle may become a fat-cell.

The fat in the interior of bones forming the yellow marrow appears to have the same general structure and to be formed in the same way as the rest of the adipose tissue.

§ **504.** The fat thus deposited in a fat-cell sooner or later disappears. It is not ejected bodily into the surrounding lymph-spaces of the connective tissue, but passes away either into the blood stream or into the lymphatics by some processes not as yet fully understood. The shell of cell-substance which forms the envelope of the fat-cell is probably of a differentiated nature, and may have properties which assist the escape of the fat; but on this point we have no exact knowledge. The disappearance of the fat appears to take place in two different ways. On the one hand, and this perhaps is the more ordinary method, the fat gradually disappears, little by little, and the rounded distended vesicle gradually assumes the characters of a connective tissue corpuscle, even of a branched one. On the other hand, especially when the disappearance is rapid and total, the space previously occupied by fat becomes filled with a clear fluid resembling lymph, the fat vesicle being transformed into a lymph vesicle. This condition however is temporary only, the lymph is subsequently absorbed and the vesicle shrinks. At times, the emptying of the cell, whether by the one method or the other, is followed by a rejuvenescence of the cell, the nucleus by division gives rise to several nuclei, and the cell divides into new cells, each of which may, under appropriate conditions, develope again into a fat-cell.

§ **505**. The fat thus lodged in adipose tissue varies somewhat in composition in various animals, but is chiefly composed of olein, palmitin and stearin in varying proportions, with small quantities of the glycerin compounds of such fatty acids as butyric, capronic, caprylic &c., together with a little lecithin and cholesterin. The 'fat' of one animal, that is the fat thus contained in adipose tissue, differs from the fat of another animal partly by the presence of more or less of one or more of these less abundant fats, but chiefly by the proportion in which the three main fats, olein, palmitin, and stearin, are respectively present in the mixed fat. The melting points of these three fats being different, the melting point of the fat of the body will differ according to the relative proportions in which the three are present. Thus the subcutaneous fat of man melts at from 15° to 22° or higher, the fat round the kidney being firmer and not melting until 25°; the fat of the dog melts at about 22°, that of the goose at about 25°, of the ox at about 40°, and of the sheep at 50°, the less resistant fat of the man and dog containing relatively more olein than that of the ox or of the sheep.

§ **506**. When we come to consider the question, By what processes does the fat make its appearance in the fat-cell? we are brought face to face with much the same kind of problem as that which occupied us in dealing with glycogen. On the one hand we may suppose that the fat is brought to the fat-cell as fat and is in some way taken up by the cell and deposited in the cell-substance with little or no change. On the other hand, we may suppose that the fat is manufactured by the fat-cell in some such way as mucin or pepsin is manufactured by a mucous or a gastric cell, out of and by means of its cell-substance, and that the process of fattening, or of producing fat in fat-cells, consists essentially in feeding and so building up the cell-substance which subsequently breaks down into fat, and does not consist merely in bringing fat within reach of the cell. Which of these views is the true one, or how far are both these operations carried on in the animal body?

In support of the latter view it may be urged that, not only the more complex living substance, but, as we have more than once urged, the simpler proteid constituent of living substance obviously contains what we may call a fatty radicle, so that we might expect fat to be formed out of its metabolism. And as a matter of fact not only in adipose tissue, but in every part of the body, living substance is continuously giving rise to and temporarily depositing in itself some amount of fat, and in what is known as fatty degeneration there seems to be evidence of the formation of fat out of proteid material.

On the other hand, we have traced the fats taken as food, and found that they pass with comparatively little change from the alimentary canal, chiefly through the intermediate passage of the lacteals, into the blood, from which they rapidly disappear after a meal. We might infer from this that an excess of fat thus entering the blood would naturally be disposed of by being simply stored up in the available adipose tissue without any further change; we can imagine that the fat, not immediately wanted by the economy, passes in some way from the blood to the connective tissue (the white blood corpuscles which appear loaded with fat after a meal possibly acting as intermediaries), and that the connective-tissue corpuscles swallow the fat brought to them after the fashion of an amœba, not digesting it but simply keeping it in store until it was wanted elsewhere.

What do experiments teach on this matter?

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In the first place, it is evident that in an animal fattened on ordinary fattening food, only a small fraction of the fat stored up in the body can possibly come direct from the fat of the food. Long ago, in opposition to the views of Dumas and his school, who taught that all construction of organic material, that all actual manufacture of living substance or even of its organic constituents, was confined to vegetables and unknown in animals, Liebig shewed that the butter present in the milk of a cow was much greater than could be accounted for by the scanty fat present in the grass or other fodder she consumed. He also urged, as an argument in the same direction, that the wax produced by bees, which though having a different composition from fat may be used as an analogy, is out of all proportion to the wax or allied bodies contained in their food, consisting as this does chiefly of sugar. And it has since been shewn in many ways that, in fattening animals, the fat accumulated in the body cannot be accounted for by the fat which has been taken in the food. It has been proved by direct analysis. Thus of two young pigs, as much alike as possible, of the same litter, one was killed and analysed, the amount of fat in the body being among other things determined. The other was fattened for a certain length of time on food whose composition was known, and then killed and analysed. It was found that for every 100 parts of fat in the food 472 parts of fat were stored up in the body during the fattening period. It is clear that fat may be formed in the body out of something which is not fat.

§ **507.** There are two possible sources of this manufactured fat. The carbohydrates of the food form one source. In treating of digestion (§ 282), we referred to the possibility of carbohydrates during digestion in the alimentary canal becoming by fermentation converted into butyric acid; and we suggested that higher and more complex members of the same fatty acid series might be obtained out of carbohydrates by somewhat analogous changes, carried on however not in the alimentary canal by means of foreign organised ferments, but in the tissues through the activity of the tissues themselves. We cannot as yet trace out the steps nor can we definitely point to any particular tissues other than the fat-cells themselves as the seats of any such changes. But there can be no doubt that carbohydrate material does in some way or other give rise to fat. A carbohydrate diet is the kind of diet most efficacious in producing an accumulation of fat in the body: sugar or starch, in some form or other, is always a large constituent of ordinary fattening foods.

Another source of fat is to be found in the proteids. We have seen that the urea of the urine practically represents the whole of the nitrogen which passes through the body. Now in any given quantity of urea the amount of carbon is far less than that found in the quantity of proteid containing the same amount of nitrogen. Thus the percentage composition of the two being respectively,

	Carbon.	Hydrogen.	Oxygen.	Nitrogen.	Sulphur.
Urea	20·00	6·66	26·67	46·67	
Proteid	53	7·30	23·04	15·53	1·13

100 grms. of urea contain about as much nitrogen as 300 grms. of proteid; but the 300 grms. of proteid contain 139 grms. (159—20) more carbon than do the 100 grms. urea. Hence the 300 grms. of proteid in passing through the body and giving rise to 100 grms. of urea, would leave behind 139 grms. of carbon, in some combination or other; and this surplus of carbon, if the needs of the economy did not demand that it should be immediately converted into carbonic acid and thrown off from the body, might be deposited somewhere in the form of fat. It has been calculated that in this way 100 grms. of proteid food might furnish 42 grms. of fat. We have already seen, in treating of the action of the pancreatic juice (§ 249), that there is evidence of a fatty element (viz. leucin, which is amido-caproic acid, and so belongs to the fatty acid series) being thrown off from the complex proteid compound in the very process of digestion; and though, as we have said, we have no proof that this action of pancreatic juice takes place largely in the normal body, its value as an example is none the less important.

Some observers have pushed this view of the production of fat out of proteids so far as to insist that all the fat formed in the body arises in this way out of proteid material, and that when carbohydrate food gives rise to the formation of fat it does so by shielding from oxidation the carbon moiety of the proteid food taken at the same time and thus permitting it to be stored up as fat. The carbohydrate itself, they argue, never becomes fat but its presence allows fat to be formed out of proteid material. This view has obviously a very important economical bearing, since, if it be true, it is useless to increase the carbohydrate material of food for the purpose of fattening, unless a sufficient proportion of proteid material be given at the same time.

The view however has been proved to be untenable by several investigations carried out on different animals. It has been shewn that an animal rapidly fattened on a diet consisting of proteids with much carbohydrate will store up far more fat than can possibly be accounted for by the proteids of the diet. Thus a dog, the fat in whose body had been reduced to a minimum by starvation, was fed for a period on measured quantities of proteids and carbohydrates, and killed. The amount of fat found after death in his body, making full allowance for the fat which remained after the starvation and for the fat accompanying the proteids in the meat given as food, was found to be far more than could be supplied by the carbon in the proteids of the food, even supposing that every jot of those proteids which did not go to make up the increase of the proteid 'flesh' of the body taking place during the fattening was used for the purpose of forming fat. Similar experiments on geese and pigs have led to similar results; and if fat be formed in this way in the bodies of carnivora and omnivora, we may be sure that the same holds good for the bodies of herbivora. We may therefore conclude that fat can be constructed in the body on the one hand out of proteid material, and on the other hand by some direct conversion of carbohydrates.

§ **508**. It is clear then that a construction of fat does occur in the body somewhere. What limits can we place on the degree to which this construction is carried? When the food contains sufficient actual fat to account for the fat stored up in the body, does any construction of fat take place? In the first place we find that when the food contains abnormal fats such as are not present in the body, spermaceti for instance, or erucin (from rape seed oil), these fats are not to be found, or are found in very small quantity, in the fat which is stored up in the body as a consequence of a large supply of that food. In the second place we may call to mind the statement previously made, that the composition of fat varies in different animals. The fat of a man differs from the fat of a dog, even if both feed on exactly the same food, fatty or otherwise. Were the fat which is taken as food stored up as adipose tissue directly and without change, recourse being had to other sources of food for the construction of fat only in cases where the fat in the food was deficient, we should expect to find that the nature of the fat of the body would vary greatly with the food. So far from this being the case, direct experiment shews that the fat of the dog is, as far as composition is concerned, very largely independent of the food, that the normal constituents of fat make their appearance very much as usual and in very much their appropriate proportion, though their proportion in the food may largely vary, and though some of them may be wholly absent. Thus in one experiment the fat of the body contained considerable quantities of stearin after a diet free from stearin, and in another preserved the normal amount of olein after a diet free from olein.

Of course it is quite possible that in such cases as these, though the stearin, or the olein, when absent from the food, was in some way or other constructed anew, yet at the same time those constituents which were present were simply stored up; and the small quantity of erucin present in the fat of the body after feeding on erucin must have been directly stored up. So also, when an animal is rapidly fattened on a diet consisting of a small quantity of proteid and a large quantity of fat, the amount of fat stored up may be too great to have come from the proteids of the diet, in which case we may infer that it was the actual fat of the food simply deposited in the fat-cells of the body. But even in this case, as more distinctly in the others, it is also open for us to suppose that all the fat taken as food was in some way or other disposed of, and that all the new fat which made its appearance was constructed anew. And the latter view is more perhaps in harmony with the histological facts previously mentioned, as well as supported by other considerations.

At the present, however, we may be content with the following conclusions. 1. Fat is actually formed in the animal body, and the fat present at any moment in the body is not exclusively, if at all, fat merely stored up from the fat of the food. 2. The carbon elements of the newly-formed fat may be supplied either from carbohydrate food, or from the carbon surplus of proteid food, or from fats taken as food which are not the natural constituents of the body-fat. 3. The fat stored up appears as fat granules or drops deposited in the cell-substance of certain cells, and the increase of the fat in the cells is accompanied first by a growth, and subsequently by a consumption of the cell-substance; but, as in the analogous case of glycogen, there is no complete evidence to shew whether the fat granules which appear are simply deposited by the cell-substance in a more or less mechanical manner, without their forming an integral portion of that cell-substance, the chief stages of the manufacture of the fat having been gone through elsewhere, or whether they arise from a breaking up, a functional metabolism of the cell-substance of the fat-cell itself; the latter view is on the whole however the more probable.

SEC. 8. THE MAMMARY GLAND.

§ 509. Since milk is a secretion, and indeed an excretion, the mammary gland ought not to be classed as a metabolic tissue, in the limited meaning we are now attaching to those words. Yet the metabolic phenomena giving rise to the secretion of milk are so marked and distinct, have so many analogies with the purely metabolic events which take place in adipose tissue, and so strikingly illustrate metabolic events in general, that it will be more convenient to consider the matter here, rather than in any other connection.

The mammary gland, formed like a sweat gland, of which it may be considered an extreme development, by an ingrowth of the Malpighian layer of the epidermis, is a compound racemose gland, constructed after the general plan of such a gland and thus composed of branching ducts ending in secreting alveoli.

The whole organ is divided by connective tissue septa into a number of lobes, in woman about twenty, each of which possesses a distinct *duct*, opening by a separate orifice on to the nipple; the gland in fact is not a single gland but several glands bound together. Each lobe is further divided by connective tissue septa into smaller lobes, and the division is repeated, the last divisions marking out small masses called *lobules.* The main duct supplying a lobe branches into a number of small ducts, each of the ultimate divisions of which ends in a lobule.

Within the lobule the duct divides into a number of relatively wide tubules which pursue a wavy or even twisted course, and bear deep lateral bulgings; these are held together by a comparatively slight amount of connective tissue. Hence in a section of a gland, each lobule appears to be composed of a number of irregularly round spaces or *alveoli*, which are the sections of the tubules and the bulgings, and which at some parts of the section appear to be closed spaces and at others to communicate with each other, or with a passage in the centre of the lobule leading to the lumen of the duct. The appearances thus presented, at least by a suckling gland, contrast markedly with those of an ordinary gland, such as the submaxillary, by reason of the large alveoli with their conspicuously wide lumina, often occupied by remains of the milk.

The ducts consist of an epithelium resting on a connective tissue basis which in the case of the main ducts is strengthened with longitudinally disposed plain muscular fibres continuous with the muscular fibres present in the dermis of the nipple. Over the greater part of their course the ducts are lined with a single layer of columnar epithelial cells, but at the mouths of the main ducts on the nipple these pass into an epidermis of more than one layer of flattened cells. Just before opening on to the nipple each main duct is widened into a flask-shaped enlargement. At the termination of the small ducts in the lobules, the columnar epithelium is said to give place to flattened cells, so that this part of the duct might be called a ductule corresponding to the ductule of a salivary gland.

§ **510**. The appearances presented by the alveoli differ widely according as the gland is one which is being used for suckling or is one in a resting or dormant condition, that is to say before any pregnancy at all has taken place or in the interval between two suckling periods. In the suckling gland each alveolus consists of a basement membrane, presenting the usual characters, lined with a single layer of cells leaving a wide lumen; but the appearances presented by the cells differ from time to time according to circumstances and are not the same in all the alveoli at the same time. We may however distinguish two conditions which, since they seem to correspond to the loaded and discharged conditions of an ordinary gland, we may call the loaded and the discharged phase respectively, conditions intermediate between the two being met with.

In the discharged phase the alveolus is lined by a layer of low cubical or even flattened cells, so that the relatively large area of the alveolus is almost wholly occupied by the lumen in which some of the constituents of the milk may still be retained. Each cell consists of granular cell-substance in which is placed a rounded or oval nucleus. Sometimes the free edge of the cell is jagged and uneven as if a portion of the free border had been torn away.

In a fully loaded phase the appearances are very different. The alveolus is now lined with a layer of tall columnar cells projecting unevenly into the lumen, the outline of which is correspondingly irregular and the area of which is much reduced. While the broader base of each cell rests on the basement membrane, the other end, conical or irregular, stretches towards the centre of the lumen. Instead of one nucleus, two or even more are now present, one well formed and normal being placed nearer the base, and the others, often shewing signs of breaking or degeneration, nearer the free end. Sometimes constrictions are seen whereby the free peripheral portion of the cell, including one or more of the nuclei, is apparently being separated from the basal portion in which the remaining nucleus is lodged; and occasionally portions or fragments of cells, nucleated or nucleusless, may be seen lying in the cavity of the alveolus. In the cell-substance, especially towards the free border of the cell, are numerous oil globules of various sizes as well as granules or particles of other nature; some of the larger oil globules may be seen projecting from the surface as if about to be extruded from the cell; and in the cavity of the alveolus oil globules with a thinner or thicker coating of cell-substance are frequently present.

Between such a fully loaded phase, and a completely discharged phase, various intermediate conditions may be observed, the cells being of greater or less height, containing one nucleus only or more than one, the cell-substance occupied with few or with many oil globules and other granules, and the free border more or less jagged.

Putting these facts together we may draw the following conclusion, which is supported by other evidence, as to the changes in the gland which characterize the loading and the discharge. During loading the low flattened cell of the discharged alveolus grows rapidly, elongating into the cylindrical form, and the nucleus gives birth to two or more new nuclei. Meanwhile active metabolism is going on in the cell-substance, deposits of fat as well as of other substances are taking place. By what seems to be of the nature of an amœboid movement, some of the oil globules (and possibly other matters) are extruded from the cell, much in the same way that an amœba extrudes its excrement. But besides this, a division of the cell, that is a separation of part of the cell-substance with an included nucleus, takes place, the daughter cell thus thrown off passing into the alveolus to form part of the milk; or a budding of the cell occurs, part of the cell without a nucleus being similarly cast off and undergoing a similar fate. In other words the secreting cell grows, loads itself with metabolic products, and when loaded gives off bodily part of itself to contribute to the secretion, part of the cell, and that part always retaining a nucleus, remaining behind in order to secure subsequent growth and further secretion.

The secretion of milk differs from such a secretion as that of saliva, and approaches the formation of sebum (§ 437) inasmuch as the transformed cell-substance is shed bodily to form part of the milk. We say form part of the milk because this gross mode of secretion is accompanied by the more ordinary mode. The cells are at the same time in the more ordinary way discharging into the lumen water holding saline and other constituents in solution. And the peculiar features of milk, as we shall see presently, correspond to this double mode of secretion. Perhaps however we ought not to call it a double mode, for the one method really passes insensibly into the other. The discharge of sodium chloride in solution from every kind of gland, of mucin from a mucous gland, of oil globules with a proteid envelope from a mammary gland, and lastly of nucleated loaded cell-substance from the mammary gland, present so many different phases of the same act of secretion.

§ **511**. The dormant resting mammary gland, that for instance of an animal which has never been pregnant, is much smaller than a suckling gland, owing to the alveoli being both smaller and less numerous. Each alveolus moreover is not a cavity lined with a single layer of epithelium, but a solid cylinder or mass of comparatively small, rounded or polyhedral cells. So long as pregnancy does not occur the growth of these is exceedingly slow, and the products of such metabolism as goes on in them are carried away by the blood, so that under normal circumstances no secretion takes place.

When pregnancy occurs rapid growth of the mamma takes place, numerous new alveoli being formed by budding, but all for a time remaining solid cylinders of cells. At the approach of the birth of the offspring, the central cells undergo metabolic changes, especially a fatty transformation, and either before or after birth are cast off, leaving a single layer to line the alveoli and to carry on the work of secretion as described above. It is generally supposed that these shed cells supply the so-called 'colostrum corpuscles' characteristic of the first milk, of which we shall speak presently. At the end of lactation an absorption of some of the alveoli takes place; and in old age still further absorption goes on with great diminution of the lumina.

§ **512**. The connective tissue, joining together the lobules of various sizes, surrounding the lobules and running in between the projecting blind ends of the alveoli within the lobules, is rich in blood vessels which form capillary networks round the alveoli; it also carries a considerable number of lymphatic vessels which arise in lymph-spaces around the alveoli and elsewhere. Leucocytes are numerous in the spaces of this connective tissue, and some of them may make their way through the basement membrane and between the secreting cells into the cavities of the alveoli and so appear in the milk.

§ **513**. *The nature of milk.* Human milk has a specific gravity of from 1·028 to 1·034, and when quite fresh possesses a slightly alkaline reaction. It speedily becomes acid; and cow's milk, even when quite fresh, is sometimes slightly acid, the change of reaction taking place during the stagnation of the milk in the mammary ducts.

The constituents of milk are:

1. *Proteids*, viz. casein, and an albumin, agreeing in its general features with ordinary serum-albumin, but which, since it is said to differ somewhat in its solubilities and rotatory power from serum-albumin, has been called *lactalbumin*. The casein, as we have seen, § 207, undergoes through the action of rennin a change whereby insoluble casein (tyrein) makes its appearance and the milk is curdled. Casein may however be precipitated in an unchanged form by saturating milk with neutral salts, or by the careful addition of acetic acid to diluted milk, or by first adding to the diluted milk a slight quantity of acetic acid and then passing through it a stream of carbonic acid. In the filtrate the presence of the lactalbumin, which occurs in small and variable quantities, may be shewn by coagulation with heat, or by precipitation with potassium ferrocyanide, &c. In the process of curdling the casein, as stated in § 207, appears to be not simply changed into tyrein but to be split up into tyrein and into another proteid, which unlike the lactalbumin is not coagulated by heat and which appears to be allied to peptone or albumose. This or a similar peptone-like body has also been found in small quantities even in milk which has not curdled; it has been called lactoprotein. The lactalbumin, though coagulated by heat when isolated, is not so coagulated as it exists in the natural milk, the alkalinity of the milk, which is increased by boiling, preventing this. Similarly casein, though coagulated by heat when simply suspended in water after being precipitated, is not coagulated by heat when it exists in a natural condition in milk; in these respects casein behaves like alkali-albumin, which it resembles in other features also. Hence milk when boiled does not coagulate as a whole, though in the superficial layers exposed to the air changes take place by which a film or skin, derived chiefly from the albumin but partly from the casein, appears on the surface; if this be removed a fresh portion undergoes the same change. The peculiar body nuclein which as we have seen, § 29, is a complex nitrogenous body differing in composition from proteids, is also present in milk in small quantities, and according to some observers is simply suspended, not really in solution, or is in some way peculiarly associated with the casein.

2. *Fats*. These are, in the main, palmitin, stearin, and olein; but other fats, supplied by butyric and other fatty acids in combination with glycerine, accompany the above in small quantities. In this respect the fat of milk resembles that of adipose tissue. Lecithin and cholesterin are also present in very small quantity, as well as a yellow colouring matter. The fat present in milk differs in different animals as to the relative proportion of olein, palmitin and stearin, and as to the kinds and relative amount of the other scantier fats.

The mixture of these fats, fluid at ordinary temperatures, is present in natural milk in the form of globules of various sizes but for the most part exceedingly small (in man from 2μ to 5μ). Milk is in fact a typical emulsion, and it is the presence of the casein in the milk which brings about the emulsion. Some observers maintain that each globule of fat is surrounded by an envelope or membrane of solid undissolved casein; but, though undoubtedly even when the fat is removed from the milk each globule remains surrounded by a layer of milk plasma, if we may so call it, rich in casein, there are no adequate reasons for thinking that the casein actually forms a membrane.

On standing a great deal of the fat collects on the top of the milk in the form of cream, but in this, as in the butter which is formed from it, the globules are still discrete, so long at least as the butter is 'fresh.' By the use of a centrifugal machine nearly the whole of the fat may be separated from the plasma.

3. *Milk sugar* or *lactose.* This is very apt to undergo fermentation into lactic acid, through the agency of an organized ferment; the milk thus becomes sour, and the casein is precipitated in a flocculent form when the acid is produced in sufficient quantity. Since the change will take place even when every care is taken to exclude germs from the atmosphere having access to the milk, the organized ferments must be present in the milk in the ducts of the gland.

4. *Salts.* Though traces of urea and kreatinin have been noted by some observers, the extractives of milk, beyond the lecithin and cholesterin already mentioned, are insignificant. The salts are of more importance; these are chiefly calcic phosphate, of whose function in the process of curdling we spoke in § 207, and potassic and sodic chlorides, with a small quantity of magnesic phosphate. Sulphates appear to be absent. A small quantity of an iron salt is present, and traces of sulpho-cyanide have been observed. Besides the phosphorus in the actual form of phosphates, milk contains a further considerable quantity of phosphorus in the proteids and in the nuclein, as well as some sulphur in the former. The inorganic constituents of milk may, broadly speaking, be said to differ distinctly from those of blood, and to much more nearly resemble those of the entire body.

The composition of milk in the same animal varies widely from time to time, and besides undergoes marked changes during the period of lactation. The relative general composition of human milk and that of the cow, the mare, and the bitch may perhaps be shewn by the following table:—but it is difficult to draw an average since the individual analyses given differ so much; the figures given for casein and fat in the milk of the bitch may be unusually high.

Average Composition of Milk in Different Animals.

	Woman.	Cow.	Mare.	Bitch
Casein &c.	2	4	2·5	10
Fats	2·75	4	2	10
Sugar	5	4·4	5	3·5
Salts	·25	·6	·5	·5
Total Solids	10	13	10	24
Water	90	87	90	76

The quantity of milk secreted by a woman in twenty hours at the height of lactation has been calculated at 700 to 800 cc. A good milch cow will yield about 10 litres of milk per diem.

§ **514**. *Colostrum.* This is the name given to the milk secreted at the beginning of a period of lactation, just before and for some days after parturition. This milk differs from the subsequent milk in microscopical characters and in chemical composition.

When ordinary milk is examined under the microscope hardly anything is seen besides the fat globules except a very few imperfect cells or portions of cells consisting of cell-substance more or less loaded with fat and containing sometimes a more or less altered nucleus. A few minute granules, thought by some to be particles of suspended casein or nuclein, are however also visible.

Colostrum on the other hand contains a large number of cells or corpuscles, which have been called 'colostrum corpuscles'. Some of these closely resemble leucocytes, others are either cells of about the same size, round or irregular, and possessing a nucleus, often misshapen, or are merely portions of cell-substance without a nucleus. In all of them the cell-substance may be loaded with fat globules or may be fairly free from fat. Some of these cells appear to be undergoing disintegration; some may at a favourable temperature exhibit slow amœboid movements, and must then at least be regarded as living.

Colostrum also differs from ordinary milk in containing not only a large quantity of albumin (lactalbumin) but also a decided amount of globulin. In consequence of this colostrum differs from milk inasmuch as it is distinctly coagulated by heat.

As stated above, during the rapid growth by which the gland is enlarged preparatory to lactation, the alveoli are at first solid masses of cells with little or no lumen, and a lumen is established subsequently by the discharge of the central cells. It is usually supposed that the cells so discharged, some undergoing much, others comparatively little change, supply the colostrum corpuscles just spoken of, and at the same time furnish the globulin and excess of albumin also characteristic of colostrum. But this is not certain. The alveoli at this time contain peculiar cells resembling colostrum corpuscles except that they are free from fat; and it is suggested that these being discharged and taking up fat in amœboid fashion become colostrum corpuscles. Some regard the colostrum corpuscles as simply leucocytes which have similarly taken up fat.

§ **515**. The mammary gland is present both in the female and the male child at birth; and in both sexes at and for a few days after birth is thrown, in common with all the other secreting glands, into secretory activity, and a small quantity of milk, the "witches' milk" so called by the Germans, is discharged from the nipple. This milk resembles in all essential features the milk of lactation. In both sexes this initial activity soon passes off, the gland in the female further developing at puberty, but in the male remaining, save in exceptional cases, in its infantile condition or somewhat retrograding.

§ **516**. *The secretion of milk.* From what has been already said it is obvious that the secretion of milk, while resembling the secretion of the other secreting glands which we have studied in being essentially an activity of the epithelium cells lining the alveoli, nevertheless presents certain interesting features special to itself. If the account given in § 510 be a true one, morphological changes in the cells are more prominent than in the case of other glands, and we may interpret the appearances there related somewhat as follows. When the discharged gland with its low epithelium begins the work of loading, the cells distinctly 'grow.' Their cell-substance increases in bulk, and elongating projects into the lumen of the alveolus. At the same time the nucleus divides as if the cell were about to give birth to new cells; but at first at all events no division of the cell-substance takes place, and the new nuclei lie imbedded in a common cell body. The cell-substance meanwhile puts on secretory activity; it deposits in itself material to form milk. The deposit of fat is conspicuous and easily recognised, but we may fairly infer that the other less easily distinguished proteid and carbohydrate materials are deposited in the cell-substance in a similar fashion. Then follows the ejection of the prepared material; and this may take place in one of two ways. The oil globules of fat may be protruded from the cell-substance much in the same way that an amœba extrudes its excrement, and possibly other constituents of milk may be ejected by a similar method. But besides this, the deferred cell division now takes place in a somewhat imperfect fashion, so that portions of the old cell carrying nuclei with them come asunder from the rest of the cell in which a nucleus is left, and lie loose in the lumen of the alveolus; portions of cell-substance free from nuclei appear also to be cast off. Here, in the lumen of the alveolus, they rapidly undergo change; the cell-substance is altered and dissolved, and its load of prepared material, probably undergoing in the act some further change, is set free, the nuclei also undergoing change and becoming ultimately broken up. Hence the constituents of milk are provided for, not only as in other glands by the material with which the cell loads itself and subsequently discharges into the lumen of the alveolus, but also by the actual substance of part of the cell itself. The characteristic nuclein of the milk has thus its origin in all probability in the shed nuclei of the secreting cells, and we may perhaps infer that the still more characteristic casein exists in milk in the form of casein and not of some other proteid in consequence of this intervention of the actual cell-substance in the formation of the milk.

It is hardly necessary to add that these bodily contributions of the secreting cell to the secretion are accompanied by that more ordinary part of secretion which consists in the flow of fluid containing various matters in solution through the cells into the alveoli, the general composition of the milk being thus secured.

§ **517**. The secretion of milk then would appear to illustrate, even more fully and clearly than do other glands, the truth on which we have so often insisted, that a secretion is eminently the result of the metabolic activity of the secreting cell. The blood is the ultimate source of milk, but it becomes milk only through the activity of the cell, and that activity consists largely in a metabolic manufacture by the cell and in the cell of the common things brought by the blood into the special things present in the milk. Experimental results tell the same tale. Thus the quantity of fat present in milk is largely and directly increased by proteid, but not increased, on the contrary diminished, by fatty food. This effect on the mammary gland in particular is in accordance with what we shall presently learn to be the general effect on the body of proteid in contrast to that of fatty food; proteid food seems to increase the general metabolic activity of the body while fatty food tends to lessen it. Moreover the proteid food seems actually to furnish the fat; and we have already suggested a manner in which proteids may give rise to fat. That the fat of the milk need not necessarily come from the fat of the food is shewn by the following experiment. A bitch fed on meat for a given period gave off more fat in her milk than she could possibly have taken in her food; and this moreover took place while she was gaining in weight and 'laying on fat,' so that she could not have supplied the mammary gland with fat by simply transferring fat from the store previously existing in the adipose tissue of her body; she apparently obtained the fat ultimately from the proteids of her food. And the histological facts given above favour the view that the formation of fat out of proteids in such cases takes place in the cells of the alveoli. The experimental then as well as the histological evidence goes to shew that the fat of milk is formed in the cell and by the cell, and is not simply gathered out of the blood.

The casein in a similar way seems to be formed by the action of the cell. It cannot be gathered out of the blood since the blood contains no real casein; it must be formed in the gland. Some observers have maintained that when milk is kept at 35°, the casein is increased through some ferment action taking place in the milk itself; but this seems not to be the case, and the formation of casein must be regarded as the result of the action of the cell. Even the albumin present appears to be not the ordinary serum-albumin simply passed from the blood through the cell into the lumen of the alveolus, but the slightly different lactalbumin. We may perhaps regard the albumin as less difficult to manufacture than the casein; and we may explain the fact that relatively to the albumin the casein is less at the very beginning and especially toward the end of lactation, by supposing that the cell has in the first case not got into full working order and in the second case is waning in power. The peptone-like body in milk though small in quantity is a further indication of the proteid metabolism taking place in the cell.

That the milk-sugar, lactose, also is formed in and by the cell, is indicated by the facts that it is found in no other part of the body, and that its presence in milk is not dependent on carbohydrate food, for it is maintained in abundance in the milk of carnivora when these are fed exclusively on meat, as free as possible from any kind of sugar or glycogen. A glycogen-like body has moreover been described as existing in the cells, and it is suggested that this body is the antecedent of the lactose.

We thus have evidence in the mammary gland of the formation, by the metabolic activity of the secreting cell, of the representatives of the three great classes of food-stuffs, proteids, fats, and carbohydrates. It is of course quite true that all the cell has to do may be simply to turn aside into the special casein, fats, and lactose, the general supply of proteids, fats, and carbohydrates brought to it in the blood, without these ever becoming actually part of the cell, the formation of fat out of proteid spoken of above taking place in some other part of the body. Still it is open for us to suppose that they are all three formed in the cell itself out of the comprehensive living cell-substance. If we accept the latter view we may look upon what is taking place in the mammary cell as a picture of what is going on in various living tissues. If the fat of the milk were not ejected from the mammary cell, the mammary gland would become a mass of adipose tissue, especially if, by a slight change in the metabolism, the production of fat were exalted at the expense of the production of casein or milk-sugar. If, again, by a similar slight change the milk-sugar were accumulated rather than the fat or proteid, we should have a result which, by an easy step, would bring us to glycogenic tissue. And, lastly, if the proteid accumulation were greater than the fatty, or the saccharine, these being carried off in some way or other, we should have an image of the nutrition of such a tissue as muscle, in which the proteid constituent is in excess of the others.

§ **518**. That both the secretion and ejection of milk are under the control of the nervous system is shewn by common experience, but the exact nervous mechanism has not yet been fully worked out. While erection of the nipple ceases when the spinal nerves which supply the breast are divided, the secretion continues, and is not arrested even when the sympathetic as well as the spinal nerves are cut.

CHAPTER V.

NUTRITION.

SEC. 1 THE STATISTICS OF NUTRITION.

§ **519**. THE preceding chapter has shewn us how wholly impossible it is at present to master the metabolic phenomena of the body by attempting to trace out forwards or backwards the several changes undergone by the individual constituents of the food, the body, or the waste products. Another method is however open to us, the statistical method. We may ascertain the total income and the total expenditure of the body during a given period, and by comparing the two may be able to draw conclusions concerning the changes which must have taken place in the body while the income was being converted into the output. Many researches have been carried out by this method; but valuable as are the results which have been thereby gained, they must be received with caution, since in this method of inquiry a small error in the data may, in the process of calculation and inference, lead to most wrong conclusions. The great use of such inquiries is to suggest ideas, but the views to which they give rise need to be verified in other ways before they can acquire real worth.

Composition of the Animal Body. The first datum we require is a knowledge of the composition of the body, as far as the relative proportion of the various tissues is concerned. In the human body the proportions by weight of the chief tissues, in the fresh state, are probably somewhat as follows:

	Adult Man.	Newborn Baby.
Skeleton	15·9 p. c.	17·7 p. c.
Muscles	41·8 „	22·9 „
Thoracic viscera	1·7 „	3·0 „
Abdominal viscera	7·2 „	11·5 „
Fat	18·2 „	20·0 „
Skin	6·9 „	
Brain	1·9 „	15·8 „

An analysis of a cat has given the following result:

Muscles and tendons	45·0 p. c.
Bones	14·7 „
Skin	12·0 „
Mesentery and adipose tissue	3·8 „
Liver	4·8 „
Blood (escaping at death)	6·0 „
Other organs and tissues	13·7 „

One point of importance to be noticed in these analyses is that the skeletal muscles form nearly half the body; we have already seen (§ 38) that about a quarter of the total blood in the body is contained in them, and have already (§ 484) insisted that a large part of the metabolism of the body is carried on in the muscles. Next to the muscles we must place the liver, for though far less in bulk than them, it is subject to a very active metabolism; this is suggested by the fact that it alone may hold about a quarter of the whole blood, and is also indicated by the numerous facts brought before us in the preceding chapter.

§ **520.** *The Starving Body.* Before attempting to study the influence of food, it will be useful to ascertain what changes occur in a body when all food is withheld. A cat of known weight was starved for 13 days. At the beginning of the period the body was presumed to have the composition given above; at the close of the period a direct analysis of the body was made. From this it appeared that during the hunger period the cat had lost 734 grammes of solid material, of which 248·8 were fat and 118·2 muscle, the remainder being derived from the other tissues. The percentages of dry solid matter lost by the more important tissues during the period were as follows:

Adipose tissue	97·0 p. c.
Spleen	63·1 „
Liver	56·6 „
Muscles	30·2 „
Blood	17·6 „
Brain and spinal cord	0·0 „

Thus the loss during starvation fell most heavily on the fat, indeed nearly the whole of this disappeared. Next to the fat, the glandular organs, the tissues which we have seen to be eminently metabolic, suffered most. Then come the muscles, that is to say, the skeletal muscles, for the loss in the heart was very trifling; obviously this organ, on account of its importance in carrying on the work of the economy, was spared as much as possible: it was in fact fed on the rest of the body. The same remark applies to the brain and spinal cord; in order that life might be prolonged as much as possible, these important organs were nourished by material drawn from less noble organs and tissues. The blood suffered proportionally to the general body-waste, becoming gradually less in bulk but retaining the same specific gravity; of the total dry proteid constituents of the body 17·3 p. c. was lost, which agrees very closely with the 17·6 p. c. dry material (almost wholly proteid) lost by the blood. It is worthy of remark that the tissues in general became more watery than in health. Similar observations on other animals have led to similar results, the chief discordance being that in some cases the bones have suffered considerable loss, in others comparatively little. We might be inclined to infer from these data the conclusions that metabolism is most active in the adipose tissue, next in such metabolic tissues as the hepatic cells and spleen-pulp, then in the muscles, and so on; but we have no warrant for these conclusions. Because the loss of cardiac and nervous tissue was so small, we must not therefore infer that their metabolism was feeble; they may have undergone rapid metabolism, and yet have been preserved from loss of substance by their drawing upon other tissues for their material. The great loss of adipose tissue is obviously to be explained by the fact that that tissue is essentially a storehouse of material, and the similarly great though less loss in the spleen and liver indicates, as indeed the facts recorded in the previous chapter suggest, that these organs too serve in part as storehouses.

During this starvation period, the urine contained in the form of urea (and that practically represents all the nitrogen of the urine) 27·7 grammes of nitrogen. Now the amount of muscle which was lost during the period contained about 15·2 of nitrogen. Thus, more than half the nitrogen of the output during the starvation period must have come ultimately from the metabolism of muscular tissue. This fact we have already used in discussing the history of urea and shall have occasion to make further use of it hereafter. The amount of urea excreted per diem has been observed in some cases to fall very rapidly during the first day or two of starvation, and then to diminish gradually, though often shewing considerable irregularities. In other cases no such large initial fall has been observed. It is most marked in animals which have been well fed before the beginning of the starvation, especially in those which have had a rich nitrogenous diet; and the discharge in these cases of an extra quantity of urea in the first day or two is obviously connected with that immediate effect of food on the excretion of urea to which we have already (§ 487) referred and to which we shall have to return in speaking of what is known as "luxus-consumption."

Comparison of Income and Output of Material.

§ **521**. *Method.* We have now to inquire how the elements of food are distributed in the excreta, in order that, from the manner of the distribution, we may infer the nature of the intermediate stages which take place within the body. By comparing the ingesta with the excreta, we shall learn what elements have been retained in the body, and what elements appear in the excreta which were not present in the food; from these we may infer the changes which the body has undergone through the influence of the food.

In the first place, the real income must be distinguished from the apparent one by the subtraction of the fæces. We have seen that by far the greater part of the fæces is undigested matter, *i. e.* food which, though placed in the alimentary canal, has not really entered into the body. The share in the fæces taken up by matter which has been excreted from the blood into the alimentary canal, is so small that it may be neglected; certainly with regard to nitrogen, the whole quantity of this element, which is present in the fæces, may be regarded as indicating simply undigested nitrogenous matter.

The income, thus corrected, will consist of so much nitrogen, carbon, hydrogen, oxygen, sulphur, phosphorus, saline matters, and water, contained in the proteids, fats, carbohydrates, salts, and water of the food, together with the oxygen absorbed by the lungs, skin, and alimentary canal. The output may be regarded as consisting of (1) the respiratory products of the lungs, skin, and alimentary canal, consisting chiefly of carbonic acid and water, with small quantities of hydrogen and carburetted hydrogen, these two latter coming exclusively from the alimentary canal; (2) of perspiration, consisting chiefly of water and salts, for the dubious excretion (see § 438) of urea by the skin may be neglected, and the other organic constituents of sweat amount to very little; and (3) of the urine, which is assumed to contain all the nitrogen really excreted by the body, besides a large quantity of saline matters and of water. Where great accuracy is required the total nitrogen of the urine ought to be determined; it is maintained, however, that no errors of serious importance arise when the urea alone, as determined by Liebig's method (which was largely used in the researches forming the basis of the present discussion), is taken as the measure of the total quantity of nitrogen in the urine, since, in this method, other nitrogenous bodies besides urea are precipitated, and so contribute to the quantitative result. It has been and indeed still is debated whether the body may not suffer loss of nitrogen by other channels than by the urine and fæces, whether nitrogen may not leave the body by the skin or indeed in a gaseous state by the lungs. The balance of the conflicting evidence seems however in favour of the view that no such loss takes place. It would appear that though nitrogen, the pivot, so to speak, of the chemical changes of living beings, forms so large a portion of the atmosphere and moreover is physically diffused through the bodies of both plants and animals, free nitrogen is of no chemical use to either of them. It enters into and remains in their bodies as an inert substance, and the nitrogen which leaves a plant or animal, in a gaseous state, is simply a part of the same inert supply and does not come from the breaking up of the nitrogenous substances of the body or of the food.

Of these elements of the income and output, the nitrogen, the carbon, and the free oxygen of respiration are by far the most important. Since water is of use to the body for merely mechanical purposes, and not solely as food in the strict sense of the word, the hydrogen element becomes a dubious one; the sulphur of the proteids and the phosphorus of the fats are insignificant in amount; while the saline matters stand on a wholly different footing from the other parts of food, inasmuch as they are not sources of energy, and pass through the body with comparatively little change. The body-weight must of course be carefully ascertained at the beginning and at the end of the period, correction being made where possible for the fæces.

It will be seen that the labour of such inquiries is considerable. The urine, which must be carefully kept separate from the fæces, requires daily measurement and analysis. Any loss by the skin, either in the form of sweat, or, in the case of woolly animals, of hair, must be estimated or accounted for. The food of the period must be as far as possible uniform in character, in order that the analyses of specimens may serve faithfully for calculations involving the whole quantity of food taken; and this is especially the case when the diet is a meat one, since portions of meat differ so much from each other. But the greatest difficulty of all lies in the estimation of the carbonic acid produced and the oxygen consumed. In some of the earlier researches this factor was neglected and the variations occurring were simply guessed at, through which very serious errors were introduced. No comparison of income and output can be considered satisfactory unless at least the carbonic acid produced be directly measured by means of a respiration chamber. And in order that the comparison should be really complete, the water given off by the skin and lungs must be directly measured also; but this seems to be more difficult than the determination of the carbonic acid.

In the plan originally adopted by Regnault and Reiset and followed by some other observers, the animal experimented on is allowed to breathe a limited and measured atmosphere. The carbonic acid, as fast as it is formed, is fixed and removed by a strong solution of caustic potash, and the normal percentage of oxygen in the atmosphere is maintained by a supply of this gas from a gas-holder. In this way both the oxygen consumed and the carbonic acid produced are *directly* determined, while the continual supply of fresh oxygen prevents any evil effects due to breathing a confined portion of air. In order however to avoid all possible errors arising from a too restricted atmosphere a different method has been adopted by Pettenkofer and Voit. Their apparatus consists essentially of a large chamber, capable of holding a man comfortably. By means of a steam-engine a current of pure air, measured by a gasometer, is drawn through the chamber. Measured portions of the outgoing air are from time to time withdrawn and analysed; and from the data afforded by these analyses, the amounts of carbonic acid (and other gases) and of water given off by the occupant of the chamber during a given time are determined. The oxygen consumed is not determined directly; but if the total amounts of carbonic acid and of water given out by the lungs and skin are ascertained and the amount of urine and fæces known, the quantity of oxygen consumed may be arrived at by a simple calculation. For evidently the difference between the terminal weight plus all the egesta and the initial weight plus all the ingesta can be nothing else than the weight of the oxygen absorbed during the period. This method in turn however is also open to objections, since minute errors in the analyses of the small samples of air employed for the determinations attain considerable dimensions when these are multiplied so as to give the changes in the whole mass of air passed through the apparatus. It seems moreover undesirable to leave the quantity used of so important an element as oxygen to be determined by indirect calculations.

Let us imagine, then, an experiment of this kind to have been completely carried out, that the animal's initial and terminal weights have been accurately determined, the composition of the food satisfactorily known to consist of so much proteid, fat, carbohydrates, salts, and water, and to contain so much nitrogen and carbon, the weight of the fæces and the nitrogen they contain ascertained, the nitrogen of the urine determined, the carbonic acid and water given off by the whole body carefully measured, and the amount of oxygen absorbed calculated—what interpretation can be placed on the results?

Let us suppose that the animal has gained w in weight during the period. Of what does w consist? Is it fat or proteid material which has been laid on, or simply water which has been retained, or some of one and some of the other? Let us further suppose that the nitrogen of the urine passed during the period is less, say by x grammes, than the nitrogen in the food taken, after deduction of course of the nitrogen in the fæces. This means that x grammes of nitrogen have been retained in the body; and we may with reason infer that they have been retained in the form of proteid material. We may even go farther and say that they are retained in the form of flesh, *i.e.* of muscle. In this inference we are going somewhat beyond our tether, for the nitrogen might be stored up as some proteid constituent of the hepatic cells or of some other tissue; indeed it might be for the while retained in the form of some nitrogenous crystalline body. But this last event is unlikely; and if we use the word 'flesh' to mean nitrogen (proteid) holding living substance of any kind, we may without fear of any great error reckon the deficiency of x grammes nitrogen as indicating the storing up of a grammes flesh. There still remain $w - a$ grammes of increase to be accounted for. Let us suppose that the total carbon of the egesta has been found to be y grammes less than that of the ingesta; in other words, that y grammes of carbon have been stored up. Some carbon has been stored up in the flesh with the nitrogen just considered; this we must deduct from y, and we shall then have y' grammes of carbon to account for. Now there are only two principal forms in which carbon can be stored up in the body: as glycogen or as fat. The former is even in most favourable cases inconsiderable, and we therefore cannot err greatly if we consider the retention of y' grammes carbon as indicating the laying on of b grammes fat. If $a + b$ are found equal to w, then the whole change in the economy is known; if $w - (a + b)$ leaves a residue c, we infer that in addition to the laying on of flesh and fat some water has been retained in the system. If $w - (a + b)$ gives a negative quantity, then water must have been given off at the same time that flesh and fat were laid on. In a similar way the nature of a loss of weight can be ascertained, whether of flesh, or fat, or of water, and to what extent of each. The careful comparison, the debtor and creditor account of income and output, enables us, with the cautions rendered necessary by the assumptions just now mentioned, to infer the nature and extent of the bodily changes. The results thus gained ought of course, if an account is kept of the water taken in and given out, to agree with the amount of oxygen consumed, and also to tally with the conclusions arrived at concerning the retention or the reverse of water.

Having thus studied the method and seen its weakness as well as its strength, we may briefly review the results which have been obtained by its means.

§ **522.** *Nitrogenous Metabolism.* When a meal of lean meat, as free as possible from fat, is given to a dog, which has previously been deprived of food for some time, and whose body therefore is greatly deficient in flesh, it might be expected that the larger part of the food would be at once stored up to supply pressing deficiencies, and that only the smaller part would be immediately worked off as urea corresponding to the nitrogenous metabolism going on in the body at the time, increased somewhat by the labour thrown on the economy by the very presence of the food. This however is not the case as far as the nitrogen of the meal is concerned; the larger portion passes off as urea at once, and only a comparatively small quantity is retained. If the diet be continued, and we are supposing the meals given to be large ones, the proportion of the nitrogen which is given off in the form of urea goes on increasing until at last a condition is established in which the nitrogen of the egesta exactly equals that of the ingesta. This condition, which is spoken of as "nitrogenous equilibrium" is attained in dogs with an exclusively meat diet only when large quantities of food are given, and is not easily maintained for any length of time. The exact quantity of meat required to attain nitrogenous equilibrium varies with the previous condition of the dog; equilibrium is frequently attained when 1500 or 1800 grms. of meat are given daily.

Thus the most striking effect of a purely nitrogenous diet is largely to increase the nitrogenous metabolism of the body; and we shall see later on that it increases the metabolism not only of the nitrogenous but also of the other constituents of the body.

The establishment of nitrogenous equilibrium does not mean that a body-equilibrium is established, that the body-weight neither increases nor diminishes. On the contrary, when the meal necessary to balance the nitrogen is a large one, the body though it is neither gaining nor losing nitrogen may gain in total weight; and the increase is proved by calculation from the income and output, and indeed by actual examination of the body, to be due to the laying on of fat. The amount so stored up may be far greater than can possibly be accounted for by any fat still adhering to the meat given as food. We are therefore driven to the conclusion that the proteid food is split into a urea moiety and a fatty moiety, that the urea moiety is at once discharged, and that such of the fatty moiety as is not made use of directly by the body is stored up as adipose tissue. And this disruption of the proteid, as we have already (§ 487) suggested, explains at the same time why the meat diet so largely and immediately increases the urea of the egesta.

This characteristic effect of proteid food to increase the metabolism of the body is shewn on other animals besides the dog, and not only by means of calculations of what is supposed to take place in the body, but also by direct analysis. Thus the analysis of the body of a pig, which had been fed on a known diet, compared with the analysis with that of another pig of the same litter, killed at the time when the first was put on the fixed diet, gave as a result that of the dry nitrogenous material of the food only about 7 p.c. was laid up as dry proteid material during the fattening period, though the amount of proteid food was low. This contrasts strongly with the amount of fat stored up during the same period (see § 506). Similar observations carried out on sheep shewed that in these animals the storing up of nitrogenous material was even less, only about 4 p.c. of that given in the food.

Every quantity of proteid material taken into the alimentary canal thus appears to affect proteid metabolism in two ways. On the one hand it excites a rapid proteid metabolism giving rise to an immediate, and generally large, increase of urea; on the other hand, it serves to maintain the more regular normal proteid metabolism continually taking place in the body, and so contributes to the normal regular discharge of urea. It seems very natural to suppose that the proteid which plays the first of these two parts is not really built up into the tissues, does not become actual living substance, but undergoes the changes which give rise to urea outside the actual living substance in the blood or elsewhere; and we have seen that under the influence of the pancreatic juice some of the proteid food may undergo the greater part of such a change while it is as yet within the alimentary canal. Hence has arisen the very natural distinction to which we have already alluded between "tissue proteids" or "morphotic proteids" which are actually built up into the living substance of the tissues and give rise to urea through the metabolism of living substance, and "circulating proteids" or "floating proteids" which do not at any period of their career within the body become an integral part of the living substance and by their metabolism set free energy not in the way of vital manifestations but in the form of heat only. We shall later on consider what is the exact meaning which we ought to attach to the words "becoming part of the living substance;" and hence shall defer until then any discussion of the appropriateness of these phrases and of the validity of the distinction which they formulate.

It was once thought, as we shall presently see erroneously, that the exclusive purpose of proteid food was to supply the proteid tissues, and that all the energy set free in the body in vital manifestations, such as movement and the like as distinguished from heat, had its origin in proteid metabolism, the metabolism of fats and carbohydrates giving rise to heat only. Hence when it first became known that a certain proportion of proteid food apparently underwent a metabolism giving rise to heat only, without becoming part of the tissues, this seemed to be a wasteful expenditure of precious material; and the metabolism of this portion of proteid food was accordingly spoken of as a "luxus-consumption," a wasteful consumption.

Before leaving this subject we may call attention to a possible analogy between the history of proteids and that of fats and carbohydrates. The uniform composition of the blood, which the body seems ever striving to maintain, probably applies to its proteids as well as to its other constituents. We have seen that a surplus of non-nitrogenous materials in the blood is withdrawn from the circulation and stored up as fat or glycogen, and it is possible that an excess of proteids might similarly be stored up in some tissue or tissues, in the hepatic cells for instance, though from the facts previously mentioned it is obvious that the power of storage is far less than in the case of fats and carbohydrates. Such a store of proteid matter would represent a sort of circulating proteid, but nevertheless for its final metabolism might have to form an integral part of some living tissue unit.

§ **523**. *The Effects of Fatty and of Carbohydrate Food.* Unlike those of proteid food, the effects of fats and carbohydrates cannot be studied alone. When an animal is fed simply on non-nitrogenous food, death soon takes place; the food rapidly ceases to be digested, and starvation ensues. We can therefore only study the nutritive effects of these substances when they are taken together with proteid material.

When a small quantity of fat is taken, in company with a fixed moderate quantity of proteid material, the whole of the carbon of the food reappears in the egesta. No fat is stored up; some even of the previously existing fat of the body may be consumed. As the fat of the meal is increased, a point is soon reached at which carbon is retained in the body as fat. So also with starch or sugar; when the quantity of this is small, there is no retention of carbon; as soon however as it is increased beyond a certain limit, carbon is stored up in the form of fat or, to a smaller extent, as glycogen. Fats and carbohydrates therefore differ markedly from proteid food in that they are not so distinctly provocative of metabolism. This is exceedingly well shewn in the results obtained on the pig previously mentioned. It was found that 472 units of fat were laid on for every 100 units of fat taken as such in the food (which consisting of barley-meal, &c. contained a very small amount of actual fat), while for every 100 units of the total dry non-nitrogenous food including fat, starch, cellulose, &c., no less than 21 units were retained in the body in the form of fat. No clearer proof than this could be afforded that fat is formed in the body out of something which is not fat. In § 507 we have already discussed this formation of fat out of carbohydrates.

As one might imagine, the presence of fat or carbohydrates in the food is found to decrease the amount of proteid material necessary to establish nitrogenous equilibrium. For instance, with a diet of 800 grms. meat and 150 grms. fat, the nitrogen in the egesta became equal to that in the ingesta in a dog, in whose case 1800 grms. meat had to be given to produce the same result in the absence of fats or carbohydrates.

On the other hand, it was found that, with a fixed quantity of fatty or carbohydrate food, an increase of the accompanying proteid led not to a storing up of the surplus carbon contained in the extra quantity of proteid, but to an increase in the consumption of carbon. Proteid food increases not only proteid but also non-nitrogenous metabolism. This explains how an excess of proteid food may, by the increase of general metabolism, actually reduce the fat of the body.

We have at present no exact information concerning the nutritive differences between fats and carbohydrates, beyond the fact that in the final combustion of the two, while carbohydrates require sufficient oxygen to combine with their carbon only, there being already sufficient oxygen in the carbohydrate itself to form water with the hydrogen present, fats require in addition oxygen to combine with some of their hydrogen. Hence in herbivora, living largely on carbohydrates, a larger portion of the oxygen consumed reappears in the carbonic acid of the egesta than in carnivora, in which animals, living chiefly on proteids and fats, more of it leaves the body combined with hydrogen to form water. This relation of the oxygen to the carbonic acid is often expressed as the quotient of the volume of the carbonic acid expired divided by the volume of the oxygen consumed, the 'respiratory quotient,' $\frac{CO^2}{O^2}$, which is in herbivora about ·9 and in carnivora about ·6 or ·7. When a herbivorous animal starves, it feeds on its own fat, and under these circumstances the respiratory quotient falls to the carnivorous standard; and indeed many circumstances affect this respiratory quotient. The carbohydrates are notably more digestible than the fats, but on the other hand the fats contain more potential energy in a given weight. As to the nutritive difference between starch and sugar, we know nothing very definite; it has been thought however that cane-sugar is rather more fattening than starch.

§ **524**. *The Effects of Gelatine as Food.* It is a matter of common experience that gelatine will not supply the place of proteids as a constituent of food. Animals fed on gelatine together with fat or carbohydrates die very much in the same way as when they are fed on non-nitrogenous material alone. Nevertheless it would appear, as might be expected, that the presence of gelatine in food is not without effect. Thus nitrogenous equilibrium is established at a lower level of real proteid food when gelatine is added. In a dog, moreover, fed on a diet of gelatine and fat, the excess of nitrogen in the excreta over that in the ingesta is less than when the same dog is fed on a diet of fat alone; that is to say, the gelatine has sheltered from metabolism some proteid constituents of the body; and the consumption of fat seems also to be lessened by the presence of gelatine. These facts become intelligible if we suppose that gelatine is rapidly split up into a urea and a fat moiety, in the same way that we have seen a certain quantity of proteid material to be. It is this direct destructive metabolism of proteid matter which gelatine can take up; it seems however unable to imitate the other function of proteid matter, and to take part in the formation of living substance; or in the phraseology of a preceding paragraph (§ 522), it can take the place of circulating but not of tissue proteid. What is the cause of this difference, we cannot at present say.

§ **525**. *Peptone as Food.* Since proteids are at least largely, as we have seen (§ 309), converted into and absorbed as peptone, and since as we have also seen the peptone appears during the very act of absorption to be reconverted into some other form of proteid matter, possibly serum-albumin, it might seem natural to suppose that peptone given as food would as far as metabolism is concerned play the same part as other proteids. Nevertheless, some observers have maintained with regard to both peptones and the allied albumoses that, like gelatine, these bodies "can take the place of circulating but not of tissue proteid." On the whole, however, the evidence goes to shew that animals can 'lay on flesh' when the proteid in their food consists entirely of peptone or albumose. A difficulty, appertaining to digestion, prevents any large substitution of peptone for ordinary proteids, since as might be expected diarrhœa is apt to be set up.

§ **526**. *The Effects of Salts as Food.* All food contains, besides the substances possessing potential energy, which we have just studied, certain saline matters, organic and inorganic, having in themselves little or no such potential energy, but yet either absolutely necessary or highly beneficial to the body. These must have important functions in directing the metabolism of the body: the striking distribution of them in the tissues, the preponderance of sodium and chlorides in blood-serum and of potassium and phosphates in the red corpuscles for instance, must have some meaning; but at present we are in the dark concerning it. The element phosphorus seems no less important from a biological point of view than carbon or nitrogen; it is as absolutely essential for the growth of a lowly being like Penicillium as for man himself. We find it probably playing an important part as the conspicuous constituent of lecithin and other complex fats belonging to the nervous system, we find it prominent in the peculiar body nuclein, we find it peculiarly associated with the proteids; but we cannot explain its *rôle.* The element sulphur, again, is only second to phosphorus, and we find it as a constituent of nearly all proteids; but we cannot foretell the exact changes which would take place in the economy if all the sulphur of the food were withdrawn. In the keratin of the epidermis and its appendages, hairs &c., it is probably undergoing excretion, though its presence in this body may have to do with the peculiar physical characters of corneous epithelium.

We know that the various saline matters are essential to health, that when they are not present in proper proportions nutrition is affected. Dogs fed on food, freed as much as possible from all saline matters, but otherwise abundant, with a proper proportion of the food stuffs, soon exhibit symptoms shewing that the metabolism of their tissues, especially of their central nervous system, is going wrong; they suffer from weakness, soon amounting to paralysis, and are often carried off by convulsions. And more or less similar derangements of nutrition follow the absence or a deficiency of individual salts. During starvation these various salts continue to be discharged from the body; in some way or other they are carried along in the metabolic stream, and their presence is in some way essential to the various metabolic processes; hence they need to be always present in daily food. In what way it is that they thus direct metabolism we do not know; we are aware that the properties and reactions of various proteid substances are closely dependent on the presence of certain salts; but beyond this we know very little. The inorganic salts are those, the nutritive value of which has been chiefly studied by experiment; but we have reason to believe that the organic salts, or extractives, which are present in greater or less quantity in all food of both vegetable and animal origin, are no less essential to the proper metabolic activities of the body. The undoubted connection of scurvy with the lack of fresh vegetable food, other conditions helping, may perhaps turn in part on this, for the evidence that the disease is due to the deficiency of potash alone is not conclusive.

Lastly, water has an effect on metabolism, as shewn, among other things, by the fact that when the water of a diet is increased, the urea is increased to an extent beyond that which can be explained by the increase of fluid increasing the facilities of mere excretion.

SEC. 2. THE ENERGY OF THE BODY.

The Income of Energy.

§ **527**. Broadly speaking, the animal body is a machine for converting potential into actual energy. The potential energy is supplied by food; this the metabolism of the body converts into the actual energy of heat and mechanical labour. We have in the present section to study what is known of the laws of this conversion, and of the distribution of the energy set free.

Neglecting all subsidiary and unimportant sources of energy, we may say that the income of animal energy consists in the oxidation of food into its waste products, viz. the oxidation of proteids, fats and carbohydrates into urea, carbonic acid and water. A principle laid down by the chemist teaches that the potential energy of any body, considered in relation to any chemical change which it may undergo, is the same when the final result is the same, whether that result be gained at one leap or by a series of steps; that, for instance, the energy set free by the oxidation of 1 grm. of fat into carbonic acid and water is the same, whatever the changes forwards or backwards which the fat undergoes before it finally reaches the stage of carbonic acid and water; and similarly, that the energy available for the body in 1 grm. of dry proteid is the energy given out by the complete combustion of that 1 grm., less the energy given out by the complete combustion of that quantity of urea to which the 1 grm. of proteid gives rise in the body. Taking this as our guide we can readily calculate the amount of potential energy contained in an average 24 hours diet, and thus obtain the average daily income of energy. For the potential energy of most of the substances used as food has been determined by direct calorimetric observations; and the several determinations, though they vary somewhat, agree sufficiently closely to serve as data for the calculations in question.

The total combustion of the following substances has given for one gramme of each substance the following results expressed in calories, that is in gramme-degree units of heat.

Meat, free from fat, 5103, and 5324. Fibrin 5511. Egg-albumin 5579. Thus, taking round numbers we may say that 1 grm. of proteid material contains 5000 or 5500 calories of potential energy, according as we use the lower or higher determinations.

Fat of beef or mutton 9069, 9365, 9423. Butter 7267 or 9192. Again in round numbers we may say that 1 grm. of fat contains about 9000 calories.

Arrowroot (nearly pure starch) 3912. Starch 4123. Cellulose 4146. Dextrose 3692. Cane Sugar 3866. Here again, taking round numbers, we shall not be far wrong in saying that the potential energy of 1 grm. of carbohydrate material is about 4000 calories.

The combustion of 1 grm. of urea sets free an amount of energy which has been determined by one observer at 2206, by another as 2465 calories. We have seen (§ 507) that 1 grm. of proteid gives rise in the body to $\frac{1}{3}$ grm. urea. Hence, to obtain the energy of 1 grm. proteid material available for the economy, we must deduct from its total potential energy, one third the potential energy of 1 grm. urea, that is, in round numbers 700 or 800 calories. This will give us 5000 – 700, or 5500 – 800, that is 4300 or 4700 calories, according as we take the lower or higher data; or we may take as a mean 4500 calories. The data then so far are as follows,

1 grm. proteid	4500	calories.
1 grm. fat	9000	„
1 grm. carbohydrate	4000	„

The average diet of an average man, that is the average amount of each food stuff respectively taken daily, may be determined experimentally or statistically. Thus a man may determine by a series of trials the diet on which, while neither losing nor gaining weight and maintaining 'nitrogenous equilibrium', § 522, he enjoys good health. Or an average may be struck of a large number of diets used by various people. We shall have something to say of this latter statistical method when we come to speak of diet. For the present purpose we may use one arrived at experimentally which we will speak of as Ranke's diet, since it was determined by a physiologist of that name from observations on himself. It was composed of 100 grm. proteid, 100 grm. fat, 240 grm. carbohydrate. Such a diet would give

100 grm. proteid (4500)	450,000	calories
100 grm. fat (9000)	900,000	„
240 grm. carbohydrate (4000)	960,000	„
	2,310,000	„

If we translate the units of heat into units of work, the 2,310,000 gramme-degree, or 2,310 kilogramme-degree calories will give us about 980,000, or, in round numbers, somewhere about *one million* kilogramme-meters.

We may, in passing, call attention to the fact that the proteids supply a relatively small part of the total energy, and that the share contributed by the large mass of carbohydrates is not much greater than that belonging to the much smaller quantity of fat. In the average diet obtained by the statistical method, in which the data are largely drawn from public institutions, the (cheaper) carbohydrates are still further increased at the expense of the (dearer) fats, a change which may tend to reduce somewhat the total energy; but this does not materially affect the broad result just given.

The Expenditure.

§ **528.** There are two ways only in which energy is set free from the body: mechanical labour and heat. The body loses energy in producing muscular work, as in locomotion and in other kinds of labour, in the movements of the air in respiration and speech, and, though to a hardly recognizable extent, in the movements of the air or contiguous bodies by the pulsations of the vascular system. The body loses energy in the form of heat by conduction and radiation, by respiration and perspiration, and by the warming of the urine and fæces. All the internal work of the body, all the mechanical labour of the internal muscular mechanisms with their accompanying friction, all the molecular labour of the nervous and other tissues, is converted into heat before it leaves the body. The most intense mental action, unaccompanied by any muscular manifestations, the most energetic action of the heart or of the bowels, with the slight exceptions mentioned above, the busiest activity of the secreting or metabolic tissues, all these end simply in augmenting the expenditure in the form of heat.

A normal daily expenditure in the way of mechanical labour can be easily determined by observation. Whether the work take on the form of walking, or of driving a machine, or of any kind of muscular toil, a good day's work may be put down at about 150,000 kilogramme-meters.

The normal daily expenditure in the way of heat cannot be so readily determined. Direct calorimetric observations on the whole body are attended with so many difficulties, except in the case of small animals, that their value is uncertain; and observations made by placing a part only of the body, an arm or leg for example, in the calorimeter, and from the data thus gained calculating the heat produced by the whole body, are subject to many sources of error.

The calorimeters usually employed in chemical operations, in measuring for instance the heat given out in chemical changes, are unsuitable for experiments on living animals. Such are the mercury-calorimeter, in which the chemical action to be studied is made to take place in the midst of a mass of mercury, from the consequent expansion of which through the heat taken up the amount of heat given out is calculated, or the ice-calorimeter in which in a similar way the heat given out is calculated from the amount of ice melted. The latter has been used for physiological purposes, but an animal surrounded by ice is under such abnormal conditions that the results are of little value. The methods usually adopted by physiologists are as follows.

In one method, the water-calorimeter, the animal is placed in a metal chamber surrounded by a jacket filled with water. The heat given out by the animal warms the water in the jacket, and the amount given out is calculated upon the increase of the temperature of the water. By supplying the animal with air through a long spiral tube passing through the water-jacket, the heat given out in the expired air is prevented from being lost.

This method may be employed in a simpler form, when the heat given out by a part of the body, the arm or leg for instance, is all that has to be determined. The part is then merely placed in a bath of water, from the changes of temperature of which the amount given out is calculated. And this modification of the method may with due precautions be employed for the whole body.

In Rosenthal's calorimeter the chamber in which the body or part of the body is placed is surrounded by, not a water-jacket, but an air-jacket, which thus serves as an air-calorimeter. The instrument consists essentially of three concentric copper cylinders; the inner one contains the animal (or other source of heat); the outer one serves merely as a casing to protect those inside from changes of temperature due to currents of air and the like; and the middle one encloses an air space between itself and the inner one. There are special arrangements for closing the cylinders after the introduction of the animal, and for supplying the animal with air for breathing purposes. With the air-jacket, or space between the inner and middle cylinders, are connected a manometer and a thermometer. When an animal (or other source of heat) is placed in the inner cylinder, the temperature and the pressure of the air in the air-jacket are increased; and from the amounts of increase measured by the thermometer and the manometer the amount of heat given out from the animal is calculated.

The calorimeters of D'Arsonval and Rubner are constructed on very similar principles.

Various attempts have been made to ascertain the amount of heat given out by the body in an indirect manner, as for instance by calculating the heat given out by the oxidation of the food. As trustworthy as any is the plan of simply subtracting the normal daily mechanical expenditure from the normal daily income. Thus, 150,000 k.-m. subtracted from one million k.-m.

gives 850,000 k.-m. as the daily expenditure in the form of heat; *i.e.* between one-fifth and one-sixth of the total income is expended as mechanical labour, the remaining four-fifths or five-sixths leaving the body in the form of heat. The results given by direct calorimetric observations and by other calculations give somewhat higher figures than these; and indeed these may probably be taken as under rather than over the true amount. In any case they are to be regarded as furnishing nothing more than a rough average, the exact amount varying according to the size, the weight, and the condition of the individual, as well as according to variations in circumstances.

§ **529.** *The Energy of Mechanical Work.* We have already in treating of muscle and elsewhere partly discussed this subject, but may here say the rest that has to be said.

The older writers, even after it had been proved that the animal body was constructive as far as the formation of fat was concerned, still held to the distinction between nitrogenous or plastic and non-nitrogenous or respiratory food. Put broadly, this view was that all the nitrogenous food went to build up the proteid tissues, the muscular flesh and the like, and that the nitrogenous egesta arose solely from the functional metabolism of these tissues, while the non-nitrogenous food was used with equal exclusiveness for respiratory or calorific purposes, being either directly oxidized in the blood or, if present in excess, stored up as fatty tissue. According to this view the two classes of income corresponded exactly to the two forms of expenditure. We have already urged several objections against this view. We have seen that in the blood itself very little oxidation takes place, that it is the active tissue, and not the passive blood-plasma, which is the seat of oxidation. We have further seen that proteid food may undoubtedly be, in the above sense, respiratory and incidentally give rise to the storing-up of fat. One division of the view is thereby overthrown. We have now to inquire whether the other division holds good, whether muscle and the other proteid tissues are fed exclusively on the proteid material of food, and whether muscular energy comes exclusively from the metabolism of the proteid constituents of muscle. We have already seen (§ 63) that when the muscle itself is examined, we find no proof of nitrogenous waste, but, on the other hand, clear evidence of the production of non-nitrogenous bodies, such as carbonic acid. And when we ask the question, Does muscular exercise proportionately increase the urea given off by the body as a whole? for this, according to the theory in question it certainly ought to do, the evidence we can obtain, though somewhat varying, gives on the whole a decidedly negative answer.

In the majority of observations no marked change at all in the amount was met with; indeed in some cases there was a distinct decrease, followed by an increase on the following days. Some observers however found a very marked increase, and this was especially the case when the subject under observation took a large amount of food and performed very severe labour. On the whole the various results obtained by different observers justify the conclusion that exercise by itself, even when severe, does not necessarily increase the amount of urea excreted, but that conditions may obtain in which such an increase undeniably occurs. We may draw the further conclusion that experiments of this kind do not supply the right method for determining the point at issue. It must be remembered that it is not the muscles alone which feel the influence of the labour; the circulation and indeed the whole body are affected by it. If we suppose a large part or even only some part of the urea to come from other than muscular metabolism, from changes in the hepatic cells for instance, we should expect that these changes, and with them the amount of urea discharged would be influenced by labour, especially by severe labour.

In no case has a direct relation between the amount of labour and amount of urea been observed. More than this, the following experience lands us in an absurdity if we suppose the whole energy of muscular work to arise from proteid metabolism. Two observers performed a certain amount of work (an ascent of a mountain) on a non-nitrogenous diet, and estimated the amount of urea passed during the period. Assuming the urea to represent the oxidation of so much proteid matter, which oxidation represented in turn so much energy set free, they found that whereas the actual work done amounted to 129·026 and 148·656 kilogram.-kilometers, for each observer respectively, the total energy available from proteid metabolism during the period was in the case of the first 68·69, and of the second 68·376 kilogram.-kilometers. That is to say, the energy set free by the proteid metabolism of the muscles engaged in the work was far less than the amount necessary to accomplish the work actually done, to say nothing of its having to provide as well for the movements of respiration and circulation. Their muscular energy therefore must have had other sources than proteid metabolism.

That on the contrary the production of carbonic acid is at once and largely increased by muscular exercise is beyond all doubt. One hour's hard labour will increase fivefold the quantity of carbonic acid given off within the hour. And in an experiment directed to this point it was found that a man in 24 hours consumed 954 grms. oxygen and produced 1284 grms. carbonic acid when doing work, as against 708 grms. oxygen consumed and 911 grms. carbonic acid produced when remaining at rest, the quantity of urea secreted being in the first case 37 grms., in the second 37·2 grms.

It is evident that the conclusions arrived at by the statistical method entirely corroborate those gained by an examination of muscle itself, viz. that during muscular contraction the expl decomposition which takes place bears chiefly, if not exclusi on the non-nitrogenous constituents of the muscle, and that it is the non-nitrogenous products which alone escape from the muscle and from the body, any nitrogenous products which result being retained within the muscle, or at least within the body. We must therefore reject the second as well as the first division of the views under discussion; not only is the muscle not fed exclusively on proteid material, but also its energy does not arise from an exclusively proteid metabolism.

Animal Heat.

§ **530.** *The Sources and Distribution of Heat.* We have already seen that the conception of the non-nitrogenous portions of food being solely calorifacient or respiratory proves to be unfounded when we attempt to trace the history of the food on its way through the body. The same view is still more strikingly shewn to be inadequate when we study the manner in which the heat of the body is produced. We may indeed at once affirm that the heat of the body is generated by the chemical changes, which we may speak of generally as those of oxidation, undergone not by any particular substances, but by the tissues at large. Wherever metabolism is going on, or to be more exact wherever destructive metabolism, katabolism, is going on, heat is being set free. In growth and in repair, in the deposition of new material, in the transformation of lifeless pabulum into living tissue, in the constructive metabolism, the anabolism of the body, and in the smaller synthetic processes of which we spoke in dealing with urea (§ 489), heat is undoubtedly to a certain extent being absorbed and rendered latent: the energy of the construction may be, in part at least, supplied by the heat present. But all this, and more than this, viz. the heat present in a potential form in the substances themselves so built up into the tissue, is lost to the tissue during its destructive metabolism; so that the whole metabolism, the whole cycle of changes from the lifeless pabulum through the living tissue back to the lifeless products of vital action, is eminently a source of heat.

Of all the tissues of the body the muscles, not only from their bulk, forming as they do so large a portion of the whole frame, but also from the characters of their metabolism, must be regarded as the chief sources of heat.

In treating (§ 65) of the thermal changes in muscle we have seen that in the total energy expended in a muscular contraction, the ratio of that which appears as heat to that which appears as external work is variable. If we take a proportion which is somewhat higher than the mean of the range there given (one fifth to one twenty-fifth), and assume that the energy involved in the work done in a muscular contraction is about one-tenth of the total energy expended, the rest going out as heat, then, upon the calculation that the total external work of the body is about one-fifth of the total energy set free in the body, it is clear that the heat given out by the muscles, even if we consider only the heat given out when they are contracting, must form a very large part of the total heat given out by the body. And even if, as recent researches indicate, the muscular machine works more economically than we have hitherto supposed, the amount of heat given out by the skeletal muscles must still remain very large. Moreover to the skeletal muscle we must add the heart which, never resting, does in the twenty-four hours as we have seen, § 138, no inconsiderable amount of work, and must give rise to no inconsiderable amount of heat. But the skeletal muscles, though frequently, are not continually contracting; they have periods, at times long periods, of rest; and during these periods of rest, metabolism, of a subdued kind it is true, but still a metabolism involving an expenditure of energy, is going on. This quiescent metabolism must also give rise to a certain amount of heat; and if we add this amount, which in the present state of our knowledge we cannot exactly gauge, to that given out during the movements of the body, it is very clear, even in the absence of exact data, that the metabolism of the muscles must supply a very large proportion of the total heat of the body. They are par excellence the thermogenic tissues.

Next to the muscles in importance come the various secreting glands. In these the secreting elements, at the periods of secretion at all events, are in a state of metabolic activity, which activity as elsewhere must give rise to heat. In the case of the salivary gland of the dog the temperature of the saliva secreted during stimulation of the chorda has been found to be as much as 1° or 1·5° higher than that of the blood in the carotid artery at the same time, and in all probability the investigation of other secreting glands would lead to similar results. Of all these various glands, the liver deserves special attention on account of its size and large supply of blood, and because it appears to be continually at work. If there be any truth in the views urged in the preceding chapter touching the large and varied metabolic work of the liver, we must conclude that a very large amount of heat is set free in this organ; and that holds good even if we make a large allowance for the various synthetic anabolic processes which may take place and by which heat would be absorbed and made latent. We find indeed that the blood in the hepatic vein is the warmest in the body. Thus in the dog a temperature of 40·73° C. has been observed in the hepatic vein, while that of the vena cava inferior was 38·35° to 39·58, and that of the right heart 37·7. The fact that the blood of the hepatic vein is warmer than that of either the portal vein or the aorta, shews that the increased temperature is not due simply to the liver being far removed from the surface of the body.

The brain too may be regarded as a source of heat, since its temperature is higher than that of the arterial blood with which it is supplied; though from the smaller quantity of blood passing through its vessels as well as from the changes in it being less massive, it cannot in this respect compare with either the liver or the muscles as a source of heat to the body.

The blood itself cannot be regarded as a source of any considerable amount of heat, since, as we have so frequently urged, the oxidations or other metabolic changes taking place in it are comparatively slight. The heat evolved by the indifferent tissues such as bone, cartilage and connective tissue, may be passed over as insignificant; and we cannot even regard the adipose tissue as a seat of the production of heat, since the fat of the fat-cells is in all probability not oxidized *in situ* but simply carried away from its place of storage to the tissue which stands in need of it, and it is in the tissue that it undergoes the metabolism by which its latent energy is set free. Some amount of heat is also produced by the changes which the food undergoes in the alimentary canal before it really enters the body.

Hence, taking a survey of the whole body, we may conclude that since metabolism is going on to a greater or less extent everywhere, heat is everywhere being generated; but that, looked at from a quantitative point of view, the muscles and the glandular organs must be regarded as the main sources of the heat of the body, the muscles being in all probability the more important of the two.

§ **531.** But heat, while being thus continually produced, is as continually being lost, by the skin, the lungs, the urine and the fæces. The blood passing from one part of the body to the other, and carrying warmth from the tissues where heat is being rapidly generated, to the tissues or organs where heat is being lost by radiation, conduction or evaporation, tends to equalize the temperature of the various parts, and thus maintains a "constant bodily temperature."

When the production of heat is not great as compared with the loss there is no great accumulation of heat within the body, the temperature of which consequently is but slightly raised above that of surrounding objects. Thus the temperature of the frog, for instance, is rarely more than ·04° to ·05° above that of the atmosphere, though in the breeding season the difference may amount to 1°. Such animals, and they comprise all classes except birds and mammals, are spoken of as cold-blooded; they have been also called poikilothermic, that is, of varied temperature. Exceptions among them are not uncommon. Some fish, such as the tunny, are warmer than the water in which they live, and in a species of Python (*P. bivittatus*) a difference of as much as 12° has been observed. In a beehive the temperature may rise at times as much as to 40°. In the so-called warm-blooded animals, birds and mammals, the loss and production of heat are so balanced that the temperature of the body remains constant at, in round numbers, 35° or 40°, whatever be the temperature of the air; hence these have been called homoiothermic, of constant temperature. The temperature of man is about 37°; in some birds it is as high as 44° (Hirundo) and in the wolf it is said to be as low as 35·24°.

This temperature is with slight variations maintained throughout life. After death the generation of heat rapidly diminishes, and the body speedily becomes cold; but for some short time immediately following upon systemic death, a rise of temperature may be observed, due to the fact that, while the metabolism of the tissues is still going on, the loss of heat is somewhat checked by the cessation of the circulation. The onset of pronounced rigor mortis causes a marked accession of heat, and when occurring after certain diseases may give rise to a very considerable elevation of temperature.

This mean bodily temperature of warm-blooded animals is, during health, maintained, with slight variations of which we shall presently speak, within a very narrow margin, a rise or indeed a fall of much more than a degree above or below the limit given above being indicative of some failure in the organism, or of some unusual influence being at work. It is evident, therefore, that the mechanisms which co-ordinate the loss with the production of heat must be exceedingly sensitive. It is obvious, moreover, that these mechanisms may act when the bodily temperature is tending to rise, by either checking the production or by augmenting the loss of heat; conversely when the bodily temperature is tending to fall, they may act by either increasing the production or by diminishing the loss of heat. As the regulation of temperature by variations in the loss of heat is better known than regulation by variations in production, it will be best to consider this first.

§ **532**. *Regulation by variations in loss.* Heat is lost to the body by the warming of the fæces and of the urine, by the warming of the expired air, by the evaporation of the water of respiration, by conduction and radiation from the skin, and by the evaporation of the water of perspiration. It has been calculated that the relative amounts of the loss by these several channels are as follows: In warming the fæces and urine about 3, or according to others 6 per cent. By respiration about 20, or according to others about 9 only per cent., leaving 77, or alternatively 85, per cent. for conduction and radiation and evaporation by the skin.

The two chief means of loss then, which are at all susceptible of any great amount of variation, and which can be used to regulate the temperature of the body, are the skin and the lungs.

The more air passes in and out of the lungs in a given time, the greater will be the loss in warming the expired air, and in evaporating the water of respiration. In such animals as the dog, which do not perspire freely by the skin, respiration is a most important means of regulating the temperature; and in the dog a very close connection may be observed between the production of heat and respiratory activity. The changes which give rise to this loss take place before the inspired air reaches the pulmonary alveoli; both the warming and the evaporation are effected in the nasal and pharyngeal, and to some extent in the bronchial passages. Some observers have maintained that the left side of the heart is warmer than the right, and hence have argued that chemical changes leading to a considerable development of heat take place in the pulmonary capillaries. It would appear however that the right ventricle, owing to its lying nearer to the liver, the high temperature of which has already been mentioned, is in reality rather hotter than the left. And indeed we have no satisfactory evidence of any large amount of heat being produced by any pulmonary metabolism.

The great regulator however is undoubtedly the skin; and this has a more or less double action. In the first place it regulates the loss of heat by means of the vaso-motor mechanism. The more blood passes through the skin the greater will be the loss of heat by conduction, radiation, and evaporation. Hence, any action of the vaso-motor mechanism which, by causing dilation of the cutaneous vascular areas, leads to a larger flow of blood through the skin, will tend to cool the body; and conversely, any vaso-motor action which, by constricting the cutaneous vascular areas, or by dilating the splanchnic vascular areas, causes a smaller flow through the skin, and a larger flow of blood through the abdominal viscera, will tend to heat the body. In the second place, besides this, the special nerves of perspiration will act directly as regulators of temperature, increasing the loss of heat when they promote, and lessening the loss when they cease to promote, the secretion of the skin. The working of this heat-regulating mechanism is well seen in the case of exercise. Since every muscular contraction gives rise to heat, exercise must increase for the time being the production of heat; yet the bodily temperature rarely rises so much as a degree centigrade, if at all. By exercise the respiration is quickened, and the loss of heat by the lungs increased. The circulation of blood is also quickened, and the cutaneous vascular areas becoming dilated, a larger amount of blood passes through the skin. Added to this, the skin perspires freely. Thus a large amount of heat is lost to the body, sufficient to neutralize the addition caused by the muscular contraction, the increase which the more rapid flow of blood through the abdominal organs might tend to bring about being more than sufficiently counteracted by their smaller supply for the time. The sense of warmth which is felt during exercise in consequence of the flushing of the skin, is in itself a token that a regulative cooling is being carried on. In a similar way the application of external cold or heat defeats its own ends, either partially or completely. Under the influence of external cold the cutaneous vessels are constricted, and the splanchnic vascular areas dilated, so that the blood is withdrawn from the colder and cooling regions to the hotter and heat-producing organs. This vascular change may be used to explain the fact that stripping naked in a cold atmosphere often gives rise to a distinct increase in the mean temperature of the blood, as indicated by a thermometer placed in the mouth, though possibly the effect may be partly due to an actual increase of the production of heat. Under the influence of external warmth, on the other hand, the cutaneous vessels are dilated, a rapid discharge of heat takes place; and if the circumstances be such that the body can perspire freely, and the perspiration be readily evaporated, the temperature of the body may remain very near to the normal, even in an excessively hot atmosphere. Thus, more than a century ago, two observers were able to remain with impunity in a chamber heated even to 127° (260° Fahr.), and with ease in one so hot, that it became painful for them to touch the metal buttons of their clothing. It is unnecessary to give any more examples of this regulation of temperature by variations in the loss of heat; they all readily explain themselves.

§ **533.** *The production of heat, its variations and regulation.* As we have already said the exact determination of the amount of heat produced in the living body is attended with great difficulties; still certain conclusions have been arrived at based partly on direct calorimetric observations, the more recent ones with improved calorimeters being especially valuable, and partly on what seem to be trustworthy deductions from observed chemical changes.

The rate of production of heat in a living body is determined by a variety of circumstances. In the first place what may be called the general rate of metabolism, and so of the production of heat, varies in different kinds of animals. Of two animals of the same bulk and weight placed under the same circumstances one 'lives faster' than the other, metabolizes its living substance more rapidly, and so produces heat more rapidly. Thus direct calorimetric observations, as far as they at present go, shew that a man on the average produces more heat, per kilo, per hour, than does a dog, and a dog more than a rabbit. Probably every species has what may be called its specific coefficient, and every individual his personal coefficient of heat-production, the coefficient being the expression of the inborn qualities proper to the living substance of the species and of the individual.

A larger living body will naturally produce more heat than a smaller living body of the same nature, since the larger body possesses so to speak a greater number of heat-producing units. But this is neutralized by an opposing tendency. The smaller body, having relatively to its bulk a larger amount of surface, loses heat at a more rapid rate than does the larger body; and therefore, to maintain the balance between loss and production, so as to secure the same constant bodily temperature (and as we have just seen the bodily temperature of warm-blooded animals is remarkably uniform), it must produce heat, per unit of its body, at a more rapid rate. As a rule the greater loss of heat owing to the relatively greater surface is so marked that of two animals having the same constant bodily temperature, of two species of mammals, or of two individuals of the same race, we should expect the smaller one to produce a relatively larger amount of heat. And direct calorimetric observations shew that this is so. The struggle for existence has raised what we have just called the specific or personal coefficient of the smaller animal.

From what we have seen concerning the immediate effects of a meal, we should be inclined to expect that food would temporarily increase the production of heat; and not only is this view confirmed by common experience and by our own sensations, but direct calorimetric observations afford experimental proof of its truth. In the dog it has been found that the rate of production increases after a meal, reaching its maximum from the 6th to the 9th hour, and then declining to a level which may be regarded as that secured by the general metabolism of the body, and which appears to be maintained with remarkable constancy until after long starvation the economy begins to break down. Thus in some experiments the production at the 9th hour, after an ordinary meal of meat and fat, was at a rate about 20 or 25 p.c. greater than that at which it was going on before food was given, and to which it subsequently sank before food was again given. It would appear that if sugar be added to the meal the rise becomes more marked at an earlier period, as if the economy found sugar easier to consume than fat. This however is a matter which as yet requires to be more fully worked out.

Labour, muscular work, has a powerful influence in increasing the production of heat. As we have seen, of the total heat produced in the body, a certain portion must always be attributed to muscular contractions which even in the most quiet body are always going on; in an ordinary active body a considerable quantity of heat must be thus generated. Hence the more active the body the greater the production of heat. As we stated before, § 87, in a contraction the proportion of the energy set free to do work to that set free as heat appears to vary under different circumstances; and the increase of heat due to labour probably varies in a corresponding way. The details of this relation have yet to be worked out, but we may at least conclude that, when a man pushes his daily labour beyond the 150,000 k.m., the additional energy thus leaving his body as work done is not taken out of the 850,000 k.m. given in § 528 as the average daily output of heat, but the total setting free of energy and the total production of heat is at the same time increased. And it need hardly be said that the figures in question give only an average estimate for a man of average build and weight, taking an average amount of average food and doing an average amount of work.

§ **534**. The production of heat thus determined by these several influences, some of which are themselves regulated by the nervous system, is further regulated in a remarkable manner. For it is not solely by variations in the loss of heat that the constant temperature of the warm-blooded animal is maintained. Variations in the amount of heat actually generated in the body constitute an important factor not only in the maintenance of the normal temperature, but also in the production of the abnormally high or low temperatures of various diseases. Many considerations have long led physiologists to suspect the existence of a nervous mechanism by which afferent impulses arising in the skin or elsewhere might through the central nervous system originate efferent impulses whose effect would be to increase or to diminish the metabolism of the muscles or other organs, and thus to increase or diminish the amount of heat generated for the time being in the body. The existence in fact of a metabolic or thermogenic nervous mechanism, comparable in many respects to the vaso-motor mechanism or to the various secreting nervous mechanisms, seems in itself *à priori* probable. And we have experimental evidence that such a mechanism does really exist.

The warm-blooded animal is distinguished from the cold-blooded animal by the fact that when it is exposed to cold or heat, it does not like the latter become colder or hotter, as the case may be, but, within certain limits, maintains its normal temperature. If the maintenance of the temperature of the warm-blooded animal during exposure to cold is assisted by an increased production of heat and is not due simply to a diminished loss, we ought to find evidence of an increased metabolism during that exposure. We ought to find under these circumstances an increased production of carbonic acid, and an increased consumption of oxygen, since it is to these products, rather than to the nitrogenous factors, on the peculiarities of which as uncertain signs of metabolism we have already insisted, we must look for indications of the rise or fall of metabolic activity. Of these two, the production of carbonic acid and the consumption of oxygen, the latter is the more important and trustworthy measure of metabolism, especially when observations are made for short periods only at a time; for as we have seen in treating of respiration the exit of carbonic acid is more closely dependent on the action of the respiratory mechanism than is the income of oxygen, and carbonic acid can be retained in loose combination and so temporarily stored up by various constituents of the body.

Taking then the consumption of oxygen, and though with less confidence the production of carbonic acid, as a measure of metabolic activity and so of heat-production, it has been shewn that a marked contrast in this respect exists between cold-blooded and warm-blooded animals exposed to changes of temperature. In the cold-blooded animal, cold diminishes and heat increases the metabolic activity of the body; as the temperature to which the animal is subjected rises or falls, so the consumption of oxygen and production of carbonic acid is increased or lessened. The body of a cold-blooded animal behaves in this respect like a mixture of dead substances in a chemist's retort: heat promotes and cold retards chemical action in both cases. Very different is the behaviour of a warm-blooded animal. In this case, within a lower and a higher limit, cold increases and heat diminishes the bodily metabolism, as shewn by the increased or diminished consumption of oxygen and production of carbonic acid as the temperature falls or rises. In these animals there is obviously a mechanism of some kind, counteracting and indeed overcoming those more direct effects which alone obtain in cold-blooded animals. And that this mechanism is of a nervous nature, is indicated by the following facts.

When a warm-blooded animal is poisoned by urari, the temperature falls and the metabolism, measured by the consumption of oxygen and the production of carbonic acid, sinks also; and that the latter is the cause, not the effect, of the former is shewn by the fact that the metabolism continues to fall though loss of heat be prevented by surrounding the animals with wrappings of cotton wool. In such a urarized animal, exposure to higher temperatures augments and exposure to lower temperatures diminishes metabolism; the urarized warm-blooded animal in fact behaves like a cold-blooded animal. Similar but perhaps not such striking or so constant results are gained by division of the medulla oblongata. After this operation the temperature of the body sinks, and the fall, though partly due to increased loss of heat by the skin, caused by the dilated condition of the cutaneous vessels, is also accompanied by diminished metabolism and is therefore in part due to diminished production of heat. And when an animal is in this condition, exposure to higher temperatures increases and exposure to lower temperatures diminishes the bodily metabolism. We can best explain these results by supposing that, under normal conditions, the muscles, which as we have seen contribute so largely to the total heat of the body, are placed, by means of their motor nerves and the central nervous system, in some special connection with the skin, so that a lowering of the temperature of the skin leads to an increase, while a heightening of the temperature of the skin leads to a decrease, of the muscular metabolism. Further, the centre of this thermotaxic reflex mechanism appears to be placed somewhere in the nervous system above the spinal cord. When urari is given, the reflex chain is broken at its muscular end; when the spinal cord is divided the break is nearer the centre. Whether we should conclude that the working of this reflex mechanism is of such a kind that cold to the skin excites the centre to a heat-producing activity, or of such a kind that warmth to the skin inhibits a previously existing automatic activity of the centre, may be left for the present undetermined.

We may add that the muscular metabolism which thus helps to regulate temperature need not involve visible muscular contractions. At the same time the heat given out by the muscles will be temporarily increased at every contraction which may occur. Thus, the shivering which follows exposure to cold distinctly helps to warm the body; indeed some observers have been led to think that, in man, this visible effect of cold plays a more important part in his heat regulation than the invisible actions which we have just described. We may also add that the regulative nervous mechanism may apparently be overborne by an exposure to too great heat or cold. When for instance the cold to which the animal is exposed becomes excessive, the reaction of the thermotaxic nervous system is powerless against the direct action on the tissues of the depressing influences, and the metabolism, together with the temperature, sinks.

The results with urari just mentioned seem to shew that this thermotaxic nervous mechanism bears chiefly on the skeletal muscles. Whether the glandular organs take any part in it, or whether they have a metabolic thermotaxic machinery of their own, of such a kind for example that the increase of heat production due to food is the result not so much of the immediate consumption of part of the food itself (luxus consumption) as of the presence of food, in the alimentary canal or after absorption, stirring up the liver to increased metabolism, we do not at present know.

§ **535**. In a number of experiments it has been shewn that injuries to, such as those caused by puncture or galvanic cautery, or electrical stimulation of limited portions of the more central portions of the brain may give rise to a great increase of the temperature of the body without producing any other marked symptom. The increase is shewn, by the increase of metabolism, increased production of carbonic acid and increased consumption of oxygen, as well as by direct calorimetric observations, to be due to an increased production of heat. This naturally suggests that the portions of the brain in question contain the hypothetical heat centre just mentioned, the lesion on stimulation exciting the centre to activity by direct action on it, instead of in the usual reflex manner. The matter has not however as yet been clearly worked out; and indeed observers are not agreed as to the exact parts of the brain injury to which, or stimulation of which, produces the effect. While some place it in the median and basal portions of the corpus striatum, others maintain that it is situated in the optic thalamus. The fact however remains that an affection of a very limited portion of the central nervous system may, without producing any other obvious effects, so increase the heat production of the body as to raise the temperature of the body several degrees.

§ **536**. By regulative mechanisms of the kind just discussed the temperature of the warm-blooded animal is maintained within very narrow limits. In ordinary health the temperature of man varies between 36° and 38°, the narrower limits being 36·25° and 37·5°, when the thermometer is placed in the axilla. In the mouth the reading of the thermometer is somewhat (·25° to 1·5°) higher; in the rectum it is still higher (about ·9°) than in the mouth. The temperature of infants and children is slightly higher and much more susceptible of variation than that of adults, and after 40 years of age the average maximum temperature (of health) is somewhat lower than before that epoch. A diurnal variation, independent of food or other circumstances, has been observed, the maximum ranging from 9 A.M. to 6 P.M. and the minimum from 11 P.M. to 3 A.M. Meals cause sometimes a slight elevation, sometimes a slight depression, the direction of the influence depending on the nature of the food: alcohol seems always to produce a fall. Exercise and variations of external temperature, within ordinary limits, cause very slight change, on account of the compensating influences which have been discussed above. The rise from even active exercise does not amount to 1°; when labour is carried to exhaustion a depression of temperature may be observed. In travelling from very cold to very hot regions a variation of less than a degree occurs, and the temperature of inhabitants of the tropics is practically the same as of those dwelling in arctic regions.

§ **537**. Many of the maladies of the body are characterized by an increase of the bodily temperature known as "fever" or "pyrexia," the thermometer very frequently rising to 39° or 40°, not unfrequently to 41°, and at times reaching 43° or even 44°; but these higher temperatures cannot long be borne without the organism failing. And as we have said, any increase in man of the bodily temperature beyond 38°, or even beyond 37·5°, indicates some disturbance. In most cases the rise of temperature has a definite objective cause, some local inflammation or suppuration, or, as in specific fevers, the presence in the economy of some "materies morbi," of the nature of an organized germ or of some other nature. We cannot here discuss the connection between the local inflammation or the specific poison and the high temperature, but we have increasing evidence that the high temperature of fever is due, not merely to a diminution of the loss of heat, though this may be a factor, but also, and indeed chiefly, to an increased production of heat. In fever, the production of carbonic acid, and the consumption of oxygen, that is to say, the metabolic changes of the tissues, are increased. The urea also is increased, and that in such a way as to confirm the view already expressed that much of the heat comes from such a metabolism of the skeletal muscles as, unlike an ordinary contraction, directly involves the nitrogenous elements. The inordinate metabolism of the body at large thus characteristic of fever is shewn by the wasting which it entails. Calorimetric observations also shew in a direct manner that the production of heat is increased. Of course mere increased production alone would be insufficient to raise the temperature of the body, for it might be met, up to a very high limit, by a compensating increase of loss of heat; but in fever this compensation is wanting, and it is perhaps this absence of due regulation which is most characteristic of the febrile condition.

In some maladies the bodily temperature falls distinctly below the normal average, reaching for instance 35° or even lower. In such cases there can be little doubt that the condition is due to diminished metabolism and diminished heat production.

One of the most marked phenomena of starvation is the fall of temperature, which becomes very rapid during the last days of life. The lowered metabolism diminishes the production of heat, and the lowered temperature in turn still further diminishes the metabolism. Indeed the low temperature is a powerful factor in bringing about death, for life may be much prolonged by wrapping a starving animal in some bad conductor so as to economise the bodily heat.

§ **538**. *Effects of Great Heat.* As we said above, the regulative heat mechanism is unable to withstand the strain of too great an external heat or too prolonged an exposure to a great but less degree of heat. The temperature of the body then rises above the normal; and it has been observed that the temperature is more easily raised by warmth than depressed by cold, at least when neither are very intense. When either in this way by external warmth or through pyrexia the temperature of the body is raised some 6° or 7° above the normal, to 45° or thereabouts, death speedily ensues. The chain of events thus leading to death has not been as yet clearly made out, and most likely the events do not take exactly the same course in all cases; but we shall probably not go far wrong in attributing death to the fact that the high temperature hurries on the metabolism of the several tissues, of some more than others, at such a spendthrift rate that their capital is soon exhausted. We have seen, § 371, that too warm blood produces dyspnœa, and soon exhausts the metabolic capital of the respiratory centre. Too warm blood similarly hurries on the beats of the heart: an explosion of the contractile substance is each time prematurely brought on before a sufficient quantity of explosive substance is accumulated, each stroke becomes more and more feeble as the rate is quickened, the beats become irregular, and finally cease. Either of these two events alone and certainly both together are enough to bring the working of the bodily mechanism to an end; but other tissues beside the heart and the respiratory centre are suffering in the same way, notably the rest of the central nervous system. This too is being hurried on unduly in its inner changes, so that not only consciousness is lost and other objective manifestations of nervous action go wrong or fail, but that regulative grasp of the central nervous system on the tissues of the body at large is loosened, and tumult takes the place of order. Whether this or that sign of disorder comes to the front, whether for instance convulsions take place, would appear to depend upon the exact turn taken by the abnormal events. In heat-stroke, more commonly known as sun-stroke, the essential condition of which seems to be a rapid rise of the temperature of the body owing to a sudden failure of the thermotaxic mechanism, the symptoms vary. Sometimes the heart suddenly gives way, at other times the respiratory centre seems to be more directly affected; sometimes convulsions make their appearance, but more commonly death takes place through a comatose condition of the brain, an initial phase of excitement of the central nervous system being not unfrequently witnessed.

Mammalian muscle, it will be remembered, § 84, becomes rigid at about 50°; but death probably always occurs before that higher temperature is reached by the blood, so that a sudden rigor mortis from heat (rigor caloris) cannot be regarded as a factor in death from exposure to too great heat. But should that temperature ever be reached by the living body, all we know leads us to infer that a sudden rigidity of the whole body would at once put an abrupt end to life; to suppose that a human body can truly register this or a higher temperature while remaining alive, to say nothing of shewing no tokens of distress, entails the supposition that such a body can differ from its fellows in its absolutely fundamental qualities, and yet make no other sign.

§ **539**. *Effects of Great Cold.* The effects of a too great lowering of the temperature of body, which is generally the result of too great external cold and rarely if ever arises from internal causes lowering the metabolism and thus the production of heat, are in their origin the reverse of those of a too high temperature. The metabolism of the tissues is lowered; and not only are the katabolic changes which lead to the setting free of energy thus affected, but the anabolic changes also share in the depression. The "living substance" falls to pieces less readily, but is also made up less readily; and could this slackening of metabolism be carried on in the several tissues at a rate proportionate to the rate at which each tissue lives, life might thus be brought to a peaceful end by gradual arrest of the life of each part of the whole body. And indeed in some cases, where the lowering of the temperature takes place gradually, something like this does occur even in warm-blooded animals. The diminished metabolism tells first and chiefly on the central nervous system, especially on the brain and more particularly on those parts of that organ which are concerned in consciousness. The intrinsic lowering of the cerebral metabolism is further assisted by a slowing of the heart beat and of the breath, drowsiness is succeeded by a condition very like to, if not identical with that known as sleep, which we shall study later on, but by a sleep which insensibly passes into the sleep of death. In some cases, however, especially those in which the lowering of the temperature is sudden and rapid, disorders of the nervous system intervene, and convulsions like those of asphyxia are produced.

§ **540**. *Hibernation.* In the majority of warm blooded-animals, the conditions thus induced by cold are rapidly fatal, and moreover in their progress very soon reach a stage from which recovery becomes impossible. In the case of some few animals, scattered members of several groups of mammalia, a similar depression of metabolism by cold is of yearly occurrence, taking place regularly as the external temperature falls in winter, and being thrown off regularly as the external temperature rises in spring. Such animals are spoken of as hibernating animals.

We are not able at present to explain why these animals behave in this way. It is obvious that for some reason they lack that power of reaction against external cold which, as we have seen, is one of the characteristics of the warm-blooded animal, but we cannot state what is the difference in their economy which leads to this lack. The 'winter sleep' is undoubtedly due to the cold of winter, and may in some cases at all events be induced by cold produced artificially in summer; but the system is predisposed and adapted to undergo the change at the appointed season, and a dormouse may fall into winter sleep at a temperature in winter higher than that at which it awakes in spring.

The phenomena of the hibernating mammal may be described as those due to a lower rate of metabolism and hence to lowered activity of the tissues in general. The heart beats very slowly, and each beat is at best of but moderate strength; and the breaths are few, feeble and far between. Respiration and circulation are thus going on, but go on so to speak at almost the slowest possible rate consistent with the continuance of the working of the economy. The breaths are, as we have said, few and far between, but they suffice to carry to the tissues the small amount of oxygen which these need and to carry off the small amount of carbonic acid which they produce. So small is the respiration of the tissues that in the depths of the winter sleep the venous blood is almost as bright as the arterial, the colour of which is nearly normal. And the small amount of destructive katabolic changes which is going on is shewn by a change in the respiratory quotient; oxygen is taken up out of proportion to the carbonic acid expired. Indeed, it has been observed that a dormouse actually gained in weight during a hibernating period; it discharged during this period neither urine nor fæces, and the gain in weight was the excess of oxygen taken in over the carbonic acid given out.

As far as regards the other functions of the body all that can at present be said is that the several fundamental activities of the various tissues, though lowered, are still continued very much as usual. The muscles and nervous elements are irritable; indeed the hibernating animal may be awaked though with difficulty by adequate stimulation; and as an instance of the fundamental similarity of the sleeping with the awake condition we may say that the slowly beating heart can during hibernation be still further slowed or be arrested by stimulation of the vagus nerve. The essential feature of hibernation in fact is that external cold is not resisted by the thermotaxic nervous mechanism, but lowers the metabolism of all the tissues, and thus lowers the functions of the whole body. When even in deep winter the hibernating animal is exposed to adequate warmth, the increased temperature awakes the tissues to increased metabolism, and the awakened animal regains the bodily temperature and acquires all the powers which it possessed in midsummer.

Preparatory to the oncoming of hibernation the body lays up unusually large stores of fat for the winter's expenditure. Many hibernating animals possess a 'hibernating gland', the cells of which become loaded with fat in the autumn and lose it during hibernation; but in all cases the great store of fat is in the adipose tissue generally. The liver of the hibernating animal, at all events of the dormouse, contains a considerable quantity of glycogen, which may be regarded as quite comparable to the hepatic glycogen of the winter frog (§ 455). The fat thus stored up before the approach of winter serves as the main supply of material for metabolism in the winter sleep. Since during the whole hibernating period some amount, at least, of oxygen is at the command of the tissues, we have no reason to think that the metabolism of hibernation is fundamentally different from the metabolism of ordinary life, or that the stored up fat suffers changes and gives rise to energy in other ways than by the oxidation which fat in an ordinary way undergoes in the body. Nevertheless a detailed study of the metabolism of hibernation accompanied by direct calorimetric observations would probably disclose interesting results.

SEC. 3. ON NUTRITION IN GENERAL.

§ 541. It may now be profitable to take a brief survey of the various conclusions at which we have arrived concerning the problems of nutrition.

We have seen that the several tissues, using lymph as a medium, live upon the blood, taking up from the blood the materials for, and returning to the blood the products of, their metabolism. The blood itself we have also seen to be replenished with food from the alimentary canal and with oxygen from the lungs, and to be freed from waste products by means of the excretory organs. In this double action the raw material of the food on the one hand undergoes, between its being placed in the mouth and its taking part in the metabolism of the tissue which ultimately uses it, many intermediate changes carried on in various parts of the body, and the waste products similarly undergo intermediate changes between leaving the tissue and appearing in the urine, the sweat or the expired air.

We have further seen reason to think that the metabolic events of the body take place in the main in the tissues, not in the blood stream on its way between the heart and the tissues. Changes, proper to the blood itself, take place in the blood; the corpuscles, red and white, with the plasma undergo like the rest of the body, their proper metabolic cycles, and in this sense blood may be called a tissue if there is any advantage in using the phrase; but, apart from these intrinsic blood changes, as far as we can see at present, the metabolism undergone during their transit along the blood channels, by the substances which are merely carried in the blood from place to place, is an insignificant part of the total metabolism of the body.

By metabolism of a tissue we understand the total chemical changes taking place in the tissue; and we divide these changes into those which either directly or indirectly are concerned in the building up, (anabolic) and those which are in like manner concerned in the breaking down (katabolic) of the living substance. We shall explain presently what we mean by the words, 'directly' and 'indirectly' used in this connection. And we may here repeat the caution (§ 30) that though for convenience sake we use the phrase 'living substance,' what is really meant by the words is not a thing or body of a particular chemical composition but matter undergoing a series of changes.

§ **542.** Since the several tissues originate through a differentiation of the simpler, primordial protoplasm, we may infer that we have a right to speak of a general plan of metabolism common to all the tissues, modified in various particulars in various tissues. It is more reasonable for instance to suppose that there is such a general plan common to both muscle and gland, than to suppose that the metabolism of the one differs wholly from or only accidentally resembles that of the other. And we may profitably take the nutrition of muscle as exemplifying, in the midst of the features special to muscle, the general plan of vital metabolism. The muscle in a normal state of things lives ultimately on the proteids, fats, carbohydrates, salts and water of the food, and on the oxygen of the inspired air, but lives directly on the blood which brings these things to it. Taking the proteids first we may ask the question, How does the blood supply the muscle with proteids?

The blood contains three classes of proteids: (1) serum-albumin, (2) globulin (paraglobulin), and (3) fibrinogen, that is to say, the body or bodies concerned in the clotting of blood, whose nature we left in § 23 as not wholly and clearly made out. With regard to the function of these three kinds of proteids in the nutrition of muscle our only conclusions at present are indirect ones, based chiefly on the results of experiments as to the relative value of these substances in maintaining or restoring the irritability of muscle. It is found that when the washed out frog's heart (§ 162) is fed with defibrinated blood, the restoration is as good as with whole blood; and that while the effects of globulin are uncertain, and while peptone and albumose appear to act in an injurious manner, the restorative effects of serum-albumin are marked. From these results we may provisionally infer that the muscle in its (total) anabolic changes takes up and so lives upon the serum-albumin of the blood. But this conclusion must be regarded as provisional only, and indeed uncertain. For we must remember that the blood supplies not only the food (including oxygen) for the muscle, but also the conditions under which the muscle can live and avail itself of the food offered to it. The complex actions through which a certain quantity of proteid and other material is built up into living muscular substance need for their execution a favourable medium, need certain physical and chemical conditions; and it may be that the favourable influence of serum-albumin is simply due to its presence in some way assisting the transformation into living substance of raw material still remaining in the muscular fibres and not to its supplying new raw material.

Dextrose is, as we have repeatedly said, always present in the blood in small quantity, and appears to be the only carbohydrate constituent of blood-plasma. Experiments carried out on a large animal, such as the horse or cow, have shewn that the venous blood coming from a muscle contains less dextrose than the arterial blood going to the muscle, and that the difference is much increased by throwing the muscle into contraction. From this we may provisionally conclude that dextrose is an essential part of the food of the muscle.

The blood as we have seen also contains a certain amount of fat; and if we push the analogy between the whole body and the muscle we may infer that the muscle takes up fat as food for itself from the blood. But we have no experimental evidence in favour of this. Moreover we have seen that fat and carbohydrate are in the animal body more or less transferable. We have distinct proof that the body can transform carbohydrate into fat; and it is very probable that it can transform fat into carbohydrate. Seeing how much more easily a soluble diffusible carbohydrate like sugar can be carried from place to place by the fluids of the body than can immiscible fats, it seems reasonable to suppose that when the body has to draw upon its store of fat in the cells of adipose tissue, the fat on leaving the fat cell is transformed into sugar, its carbon so to speak being dealt out to the tissues in the form of dextrose. Indeed we may perhaps, dwelling on the fact that a muscle though itself essentially of proteid build, turns over (§ 87) in its daily work so much more carbon than nitrogen, entertain the view that what muscle wants as food is a certain amount of proteid plus an additional quantity of carbon in some form or other, and that dextrose is a convenient form in which the additional carbon can be supplied. And we may hold this view without prejudice to any opinion that the carbon so brought, while being built up into the living substance, may be again arranged as fat, and in the course of the metabolism of the muscle may be later on separated from the living substance and deposited in the fibre as globules of fat. But our knowledge is at present insufficient to decide whether this view is true or no.

The various salts brought to the muscle by the plasma, though they supply no energy are as essential to the life of muscle as the energy-holding proteid or carbon compound; and experiments made with regard to some of them, calcic salts for instance, shew that their presence or absence materially affects the maintenance or restoration of irritability. Some of these probably play the part only of securing by their presence favourable conditions for the due metabolic processes, somewhat after the way in which the presence of calcic phosphate determines the curdling of milk; but some we probably ought to regard as actually entering into the processes themselves. Of these matters however we know very little.

§ **543**. The end-products of muscular metabolism are as we have seen carbonic acid, lactic acid, and kreatin or some other nitrogenous bodies, and we have already (§ 87) said all we have to say concerning the formation of these products. We may however briefly consider here the question, what is the relation of these various metabolic processes to the structural elements of the tissue? When we say that the muscular fibre is continually undergoing metabolism do we mean that every jot and tittle of the fibre is undergoing change and that at the same rate? We can hardly suppose this. It seems unlikely, for instance, that the metabolism of the fibrillar substance is identical with that of the interfibrillar substance, whatever be the view we take as to the properties or meaning of the two substances. Further, if we accept the suggestions made in § 87 as to a contractile substance, which, though having peculiar qualities, being peculiarly related to and having peculiar connections with the rest of the fibre, may in a broad way be compared with the glycogen of a hepatic cell, we can conceive that this contractile substance may be manufactured without the whole of it at least having been at any time an integral part of what we may in a stricter sense call the real living substance of the fibre. We should thus be led to regard the metabolic events occurring in muscle as falling into two classes at least; those taking place in the living more permanent framework, and those bearing on the formation and destruction of the contractile substance lodged in that living framework. Further, if we suppose that the metabolism by which the muscles supply so much of the heat of the body, and which as we have seen may and does go on independently of contractions, is not a metabolism of the same contractile substance differing from the metabolism of a contraction in being so ordered that all the energy goes out as heat, none being employed to effect a change of form, but is a metabolism of some other 'thermogenic' substance, we should have to add a third class to the other two. These of course are at present matters of speculation; but on the whole the evidence we can gather tends and perhaps increasingly tends to shew that in muscle there does exist such a framework of what we may call more distinctly living substance which rules the histological features of the fibre, and whose metabolism though high in quality does not give rise to massive discharges of energy, and that the interstices so to speak of this framework are occupied by various kinds of material related in different degrees to the framework and therefore deserving to be spoken of as more or less living, the chief part of the energy set free by muscle coming directly from the metabolism of some or other of this material. And the same view may be extended to other tissues. Both the framework and the intercalated material undergo metabolism, and have, in different degrees, their anabolic and katabolic changes; both are concerned in the life of the living substance, but one more directly than the other, and this is what was meant by the terms 'directly' and 'indirectly', used in § 541. Such a mode of expression seems preferable to the more common one, based on the analogy of a firearm, of the muscle fibre firing off the contractile material; in the firearm there are no such connections between the machine and the charges as obtain in the living mechanism. We may perhaps further be led by this to distinguish between growth as bearing on the framework, and more temporary nutrition as bearing on the accumulation and expenditure of the lodged material. We may add that since some of the material so lodged in the framework will consist of substances which have not yet undergone metabolism, but are either about to be worked up into the framework itself, or are about to be transformed in a more direct way into some product of metabolism, or are substances whose presence is in some way necessary for the carrying on of metabolic processes in which they themselves take no bodily part, we must recognize a continuity without any sharp break between this material which we regard as part of the tissue, and the lymph which simply bathes the tissue and flows through its interstices. Hence such phrases as 'tissue proteid' and 'floating proteid', § 522, are undesirable if they are understood to imply a sharp line of demarcation between the "tissue" and the blood or lymph, though useful as indicating two different lines or degrees of metabolism.

§ **544**. The products of muscular metabolism pass into the lymph bathing the fibre and so, either by a direct path into the capillaries or by a more circuitous course through the general lymphatic system, into the blood. The fate of the carbonic acid we have fully treated of in dealing with respiration; the little we know concerning the nitrogenous product or products has been stated in dealing with urea; the third recognized product is lactic acid, sarcolactic acid. Did any considerable amount of oxidation take place in the blood stream while the blood is flowing along the larger channels, subject only to the influence of the vascular walls, we might fairly expect that the lactic acid discharged from the muscles would be subjected to oxidising influences while still within the blood stream of the larger channels. We have however no satisfactory evidence of any lactic acid being oxidised in this way. On the contrary, there is a certain amount of experimental and other evidence that lactic acid present in the blood is somehow or other disposed of by the liver; and that if the liver fails to do its duty lactic acid may appear in the urine. It is tempting to suppose that it might there by a synthetic effort be converted into glycogen, the liver thus utilizing some of the muscular waste product, but the experimental and other evidence is all against this view. In fault of actual knowledge we are led to infer that it is in the liver oxidized into carbonic acid and water, thus adding its contribution to the supply of heat, or prepared in some way for oxidation elsewhere. Probably such a change is not confined to the liver, but takes place in other organs such as the spleen. Thus the kind of action on which we dwelt in treating of urea, namely that the products of the metabolism of one organ are carried to other organs for further elaboration and possible utilization applies to the non-nitrogenous as well as to the nitrogenous products of muscular metabolism; and if a muscle gives rise to other non-nitrogenous products than carbonic and lactic acid these are probably disposed of in some such way as the lactic acid. In speaking of glycogen in the winter frog (§ 460) we said that possibly the glycogen so stored up might arise from sugar brought to the liver from other tissues. If that be so, we should further expect that some at least of that sugar, either as such or as some allied substance, would come from the skeletal muscles which form so large a part of the body of the frog; and if so, we must conclude that under the special circumstances obtaining in the winter frog the muscles discharge into the blood a non-nitrogenous product not in the form either of carbonic or lactic acid. It is perhaps however more probable that the sugar in question comes from a metabolism of the fat stored up in the 'fatty bodies' and elsewhere.

§ **545**. As far as we can see at present the plan of nutrition thus briefly sketched out for muscle holds good for the other tissues as well, the chief or at least the most conspicuous differences bearing on the nature and properties of and the changes undergone by the material formed by and held by the more distinctly structural framework. Thus the mucin of the salivary mucous cell finds its analogue either in the contractile substance itself, or more probably in some early nitrogenous product of the explosion of the contractile substance, such as may correspond to the myosin of rigid muscle. The metabolism of the hepatic cell seems as we have seen to be especially characterised by its returning to the blood a body, viz. sugar, still containing a considerable amount of energy, available for use in other parts of the body. And this suggests the question whether in the normal metabolism of muscular substance a similar something, still holding a considerable quantity of energy, some proteid substance for instance, may not be returned to the blood; so that the metabolism of muscle is imperfectly described in saying that the results are carbonic and lactic acids and an antecedent of urea. If this be so, then muscles may be of other use to the body at large than as mere contractile machines, just as the liver has other uses than the production of bile. And the same considerations may be applied to the other tissues as well.

§ **546**. Whether the chief product of the metabolism of any tissue be a proteid substance, or a fat, or a carbohydrate, proteid substance is the pivot so to speak of the metabolism, and nitrogenous bodies alway appear as the products of metabolism. This is strikingly seen in the nutrition of plants where, as far as mere bulk or weight is concerned, the active metabolizing tissue is insignificant compared with the mass of products of metabolism heaped up in the form of starch or cellulose or some allied carbohydrate. The protoplasm of a vegetable cell soon becomes a mere film bearing a heavy burden of heaped up metabolic products and eventually disappears; and of that film only a part corresponds to what we spoke of above as the living framework of the muscle. Yet that scanty proteid-built framework is more or less directly concerned in the production of the carbohydrate material and the various conversions which that material undergoes. Proteid, nitrogen, changes are entangled with the carbon changes; and since the products of metabolism in the plant are not as in the animal cast out of the organism, but for the most part heaped up within it, we find the plant storing up in parts, where if they serve no useful purpose they at least do not harm, nitrogenous products of metabolism, such as those known as vegetable alkaloids, many of which by their amide nature betray their kinship to the animal nitrogenous product urea.

§ **547**. The rate at which in the adult, leaving aside for the present the special nutrition of the young, nutrition is carried on, and the characters of the nutrition, are dependent on a variety of circumstances. Each tissue has of course a line of nutrition of its own which circumstances may favour or hinder but cannot change in nature; the nutrition of the hepatic cell cannot be altered to that of the muscular fibre. The same tissue moreover has in different races and different individuals specific and individual characters of nutrition; the flesh of the dog is not the same as that of a man, the muscle of one man lives differently from that of another, the metabolism per unit of body weight is as we have seen greater in the smaller organism, and so on.

Within the limits and subject to the conditions however thus fixed by race and personality, general influences produce general variations in nutrition. The rate of nutrition of a tissue for instance is dependent on the food, on the amount and nature of the food material brought to the tissue by the blood. We have seen that proteid food, in contrast to carbon food markedly increases the metabolism of the body. Since this increase tells not only on the nitrogenous but also on the carbon metabolism (§ 523), it cannot be the result of a mere luxus consumption of the proteid food itself; and unless we suppose that the presence of the excess of proteid material either in the alimentary canal, or while passing through the capillaries of some organ such as the liver, acts as a stimulus to some reflex nervous machinery through whose action the metabolism of certain or of all the tissues is hurried on, we must conclude that it is the direct access of proteid material to the tissues themselves which stirs them up to increased metabolic activity. That proteid food should do this, and not carbohydrate or fat, seems to be connected with the fact just dwelt on that proteid material is the pivot of metabolism.

§ **548**. In the preceding chapters of this work we have had abundant evidence that the metabolism of the tissues is subject to the government of the central nervous system; the contraction of a muscle, the secretory activity of a gland, the increased or diminished production of heat all afford instances of nervous impulses affecting metabolism. In most of these instances the changes induced fall within the downward, katabolic, phase and have a downward character; thus when a muscle contracts, the result is a conversion of more complex bodies into simpler bodies; and the same as far as we can see is true of most other cases. But it is open for us to suppose that nervous impulses might affect the upward, anabolic, phase and have a constructive influence. There are no reasons for regarding such an action as impossible; and indeed some phenomena, such as those of inhibitory nerves and the antagonism between these and augmentor nerves, pointedly suggest some such view. Thus we may suppose that an inhibitory impulse produces such changes in the cardiac muscular substance that the upward constructive processes are assisted and the downward disruptive processes checked, whereby the setting free of energy is checked and so the beats hindered or stopped, the immediate inhibitory effect being followed by a period of rebound in which the savings of the inhibited period are spent in increased action. Conversely we may suppose that an augmentor impulse hinders the anabolic and assists the katabolic changes, and conversely also when it has done its work leaves the tissue with diminished capital manifested by feebler beats or by the absence of the power to beat. And similarly in the case of the respiratory centre and of other tissues. When we have to study the origination of visual impulses in the retina we shall come upon a view that a wave of light may affect what we shall call a visual substance either by promoting anabolic constructive changes or by increasing katabolic destructive changes according to its wave length. There is then evidence to a certain extent for the view on which we are dwelling; but, without discussing the matter any further, we may say that the conception though suggestive has not yet been demonstrated and so far can only be spoken of as probable.

§ **549**. One value perhaps of such a view lies in the fact that it warns us against assuming that a nervous impulse can only produce disruptive katabolic changes such as are seen in muscular contraction or in secretion. The effects of stimulating a nerve going to a muscle or a salivary gland are striking and obvious, and the behaviour of a muscle or a gland as far as contraction and secretion are concerned is, within certain limits, under experimental control. But there are certain phenomena, seen chiefly in the course of disease, and lying, to a very small extent only, within the control of experiment, which seem to shew that the central nervous system governs the metabolic changes, the nutrition, not only of muscle and gland, but of various other tissues in a deeper and more general way than that of simply promoting (or hindering) contraction or secretion. Thus as we have seen (§ 83) when the connection between a muscle and the central nervous system is severed, the muscle eventually wastes and loses its vitality; when all the nerves going to the sub-maxillary gland are severed, the gland instead of being as in the normal condition intermittently active and quiescent, pours forth a continuous "paralytic" secretion and eventually degenerates and wastes. When in a rabbit the fifth nerve is divided in the skull the loss of sensation in those parts of the face of which it is the sensory nerve is followed by nutritive changes. Very soon, within twenty-four hours, the cornea becomes cloudy; and this is the precursor of an inflammation which may involve the whole eye and end in its total disorganization. At the same time the nasal chambers of the side operated on are inflamed, and very frequently ulcers make their appearance on the lips and gums. And similar results have been seen in other animals including man. If the operation be conducted in a young animal, which subsequently lives to maturity, the head may become bilaterally unsymmetrical, as shewn especially by the skull. Again division of both vagus nerves is very apt to be followed by inflammation of both lungs, by fatty degeneration of the heart, and so by death.

In several of these instances the effect is a mixed one and the problem complicated. Thus, in the case of division of the fifth nerve, seeing how delicate a structure the eye is, and how carefully it is protected by the mechanisms of the eyelids and tears, it seems reasonable to suppose that the inflammation in question might simply be the result of the irritation caused by dust and contact with foreign bodies, to which the eye, no longer guided and protected by sensations, these being destroyed by the section of the nerve, became subject. In the same way the ulcers on the lips and gums might be explained as injuries inflicted by the teeth on those structures in their insensitive condition. And some observers maintain that the inflammation of the eye may be greatly lessened or altogether prevented if the organ be carefully covered up and in all possible ways protected from the irritating influences of foreign bodies. Other observers however have failed to prevent the inflammation in spite of every care. So also the inflammation of the lungs following upon division of both vagus nerves seems to be due not to any direct nutritive action of the pulmonary branches of the vagus on the pulmonary tissue, but to food accumulating in the pharynx owing to the paralysis of the œsophagus and larynx, and then passing into the air passages and so setting up inflammation. Death in these cases is moreover often the simple result of inanition caused by the paralysis of the œsophagus allowing no food to reach the stomach. The phenomena of the paralytic secretion of saliva are also of a complicated nature.

But even without insisting on such instances as the above, various other phenomena of disease seem to indicate such an influence of the nervous system on nutrition as we are discussing. As examples we might mention the rapid and peculiar degeneration of and loss of contractility in the skeletal muscles in certain affections of the spinal cord, the changes in the muscles being more rapid and profound than in the nerves; the phenomena of bed-sores, especially the so-called acute bed-sores of cerebral apoplexy; some at least of the cases of vesical affections attendant on spinal or cerebral diseases or injuries; the more rapid atrophy and loss of contractility in muscles which follow upon contusions of nerves as compared with the effects of simple section of nerves; the occurrence of certain eruptions, such as lichen, zona, ecthyma, &c., in various spinal or cerebral diseases, and indeed the general phenomena, and especially the topography of the eruption, of a large number of cutaneous diseases. Lastly but not least we might quote the general process of inflammation. These are examples of disordered nutrition. To them we might add as instances of altered but yet orderly nutrition the remarkable connections observed between changes in the form of the fingers and growth of the nails and hairs, and certain internal maladies, such for instance as the 'clubbed fingers' of pthisical and other patients, and the like. We might also call attention to the influence of light on the nutrition of animals. The experience of blind people and blind animals indicates some special connection between visual sensations and the nutrition of the skin; and this can hardly be other than a nervous connection. The effects of prolonged darkness on nutrition in general and the experimental results which shew that the total metabolism of the body is influenced by light, also suggest some nervous action. The influence of cold again in determining the growth of hair points in the same direction.

Making every allowance for the intervention as factors in the production of the phenomena quoted above of such common actions of the nervous system as are already well known to us, such as vaso-motor changes, making every allowance for the consequences of the failure or bluntness of sensation and the absence of those beneficial after results of muscular activity which we pointed out in § 86, recognizing moreover that changes in one organ may affect the condition of other distant organs by changes induced in the composition or qualities of the blood, there still remains a residue which seems distinctly to point to the conclusion that the influence of the nervous system is not limited to such changes of the muscles as belong to the production of contractions or the generation of heat, but bears on the whole nutrition of the muscle. Similar considerations lead us also to conclude that the influence of the nervous system bears on the whole nutrition of the glands, of the blood vessels, of the skin and the connective tissues in general, in fact of nearly the whole body.

Such an influence of the nervous system has often been spoken as 'trophic;' and the term has often been used as if the growth and nourishment of a tissue were the result of nervous action, or at all events could not be complete without the intervention of nervous impulses. Hence, in this view, the consequences following upon section of the fifth nerve as regarded as due to the falling away of 'trophic' influences. Such a view has however no sound basis. All biological studies teach us that the growth, repair, and reproduction of living substance may go on quite independently of any nervous system. The white blood corpuscles go through their cycles unmoved by nervous impulses, and the nutrition of the nervous system itself cannot be dependent on the action of that system on itself. All that is really needed to explain these phenomena is an acceptance of the view that a nervous impulse may modify the metabolic events of other tissues than muscles and glands, and may modify them in various ways; and further that the nutrition of each tissue is in the complex animal body so arranged to meet the constantly recurring influences brought to bear on it by the nervous system, that, when those influences are permanently withdrawn, it is thrown out of equilibrium; its molecular processes, so to speak, then run loose, since the bit has been removed from their mouths. And as our knowledge of metabolic processes on the one hand and of the actions of the nervous system on the other hand increases, these suppositions become more and more reasonable.

SEC. 4. ON DIET.

§ **550**. An ordinary man living an ordinary life will need for the maintenance of vigorous health a certain amount of food of a certain kind; this we may take as a normal diet.

Presuming that the experience of man has led him to adopt what is good for him, we may ascertain approximately the normal diet by means of the statistical method, by examining the nature and amount of the daily food of a very large number of individuals. The most valuable data for this purpose are those gained by inquiries among persons who choose their own food; the results gained from the diets used in prisons or other institutions, or among bodies of men such as the army, though more readily arrived at, are open to the objection that the diets in question are determined in part by the theoretical opinions of those whose duty it is to fix the diet. Putting together the various statistical results thus obtained, and selecting the quantities which seem to be most commonly used rather than attempting to strike a strict average or take a strict mean, we find that in an ordinary diet for the twenty-four hours the several food-stuffs are

Proteids from 100 to 130 grms.
Fats „ 40 „ 80 „
Carbohydrates 450 „ 550 „

to these we must add

Salts 30 grms.
Water 2800 „

The total (available) potential energy of the lower estimate is 2610, of the higher 3505 (kilogramme-degree) calories, calculated, in round numbers, on the data of § 527. With such a statistical diet we may compare an experimental diet, that is to say a diet arrived at through a series of trials on an individual man whose body might be taken to be an average one, that diet being considered a normal one in which the body, maintaining vigorous health, neither gained nor lost in weight, and remained moreover in nitrogenous equilibrium with the nitrogen of the egesta equal to that of the ingesta. To make sure that under such a diet the body was remaining of the same composition there ought to be evidence of a carbon equilibrium also, otherwise during the period of the experiment fat might be being replaced by water (see § 521); but this is unlikely, and we may therefore accept the method as a fair one. It has given in the hands of two different observers the following somewhat different results, the diet A being that already quoted in § 527:

	A		B
Proteids	100	grms.	118
Fats	100	„	56
Carbohydrates	240	„	500
Salts	25	„	—
Water	2600	„	—

The total (available) potential energy is respectively 2310, and 3035 calories.

On the whole the diets gained by the two methods agree very largely. To put down a single column of figures as "*the* normal diet" would be to affect a vain and delusive accuracy. If we desire, for theoretical purposes, to select some one set of figures rather than others, we might be influenced by the considerations that the lower amount of proteids in the experimental diet was nearer the mark than the higher amount of some of the statistical diets, and further that, where cost is not of moment, the substitution of fat for an excess of carbohydrates is desirable. We should be thus led to take the experimental diet A as on the whole the best or most 'normal' one, and that is the one which we employed in the calculations of § 527. It will be observed that the potential energy of this diet is less than that of any of the others, and, as we said while then speaking of it, may be considered low; but there was no evidence that it was insufficient. Still it must be remembered that neither it nor any of the others is to be regarded as distinctly proved to be the real normal diet. Against the experimental diet we may urge that the number of experiments have been few and conducted on a few individuals only at most, and that a larger number of experiments, with a variety of combinations of different amounts of the several food-stuffs, might lead to a different result; that for instance with certain amounts of fats and carbohydrates, the amount of proteid needed to maintain healthy bodily equilibrium, including nitrogenous equilibrium, might be reduced much below the 100 grammes, especially if particular kinds of proteids, fat or carbohydrates were used, and especial attention (see § 526) were paid to the salts. And indeed a considerable number of observations have been made tending to shew that a man of average size and weight may continue in nitrogenous equilibrium and in good health with a daily ration of much less than 100 grm. proteid, with as little as 40 grm. for example. To this we shall have to refer in speaking of a vegetable diet. Against the statistical diet on the other hand we may urge that instinct is not an unerring guide, and that the choice of a diet is determined by many other circumstances than the physiological value of the food.

§ **551**. Taking however some such diet as the above to be the approximately true normal diet, we may call attention to the fact that the normal diet is made up of each of the three great food-stuffs, carbohydrates being in excess. We may here remark incidentally that the diets of both the carnivora and herbivora agree with that of omnivora in containing all three food-stuffs: they differ from each other as to the relative proportions only. As we have seen, the body may be maintained in equilibrium on proteid food alone; but an exclusively proteid diet is not only bought dearly in the market, but also paid for dearly within the economy; we are of course now speaking of man. To obtain the necessary carbon out of the carbon moiety of proteid unnecessary labour is thrown on the economy, and the system tends to become blocked with the amides and other nitrogenous waste arising out of the nitrogen moiety simply thrown off to secure the carbon.

Fats and carbohydrates are much more akin to each other than is either to proteid; and if on the one hand, as (§ 542) seems possible or even probable, the fat of the food and of the body is converted into sugar either on its way to become built up into the tissue or in the course of the changes taking place outside the real living framework of the tissue by which it is reduced to carbonic acid, and that on the other hand carbohydrates can furnish the fat whose presence in the body is necessary, we might expect that carbohydrate alone without fat might, with proteid, form a normal diet. But on this point experience is probably to be trusted; and we may infer that in every normal diet some fat at least must be added to the starches and the sugars.

The advantage of this mixture is probably felt while the food is as yet within the alimentary canal. What we have learnt concerning digestion leads us to regard it as a complicated process, and we cannot readily imagine that the proteolytic, amylolytic and adipolytic changes run their several courses, especially in the small and large intestine, apart from and irrespective of each other. We are rather led to suppose that the accompaniment of one set of changes, in some indirect manner, favours the others; and it is for that reason probably that we take our food-stuffs not separately but mixed in the same meal, often on the same plate and even in the same mouthful. But apart from this the two food-stuffs, fats and carbohydrates, must play different parts in the economy, so that the one cannot be wholly substituted for the other; and though, beyond the fact that the one seems to be a source of energy and the other not, we do not as yet know the true physiological function of the hydrogen of the fat as compared with that of the differently disposed hydrogen of the carbohydrate, we may perhaps infer that the difference of use within the body of the two kinds of food-stuffs bears not so much on their ultimate consumption to supply energy as on the various complicated processes which they undergo and arrangements in which they take part before the end of their work is reached. We have had a hint that the carbohydrate more rapidly supplies the heat-giving metabolism than does the fat; and this suggests an advantage to the economy in receiving daily a certain portion of the more tardy material, while at the same time it may be taken to mean that the fat before it is used to give rise to energy has first to be converted into sugar, and so takes more time in its work.

The main carbohydrate of every diet is starch, and as far as we can learn at present, the starch which is so large a part of the cereals and vegetables consumed by man is the same body in all of them; for the use of such bodies as inulin is so insignificant that it may be neglected. Man however consumes no inconsiderable quantity of sugar, chiefly cane sugar. Since the starch of a meal does not become available for the economy until it has been converted into sugar, we might be inclined to infer that it was a matter of indifference whether the carbohydrate of a diet were supplied as starch or as sugar. But besides the fact that any large deficit of starch in a diet might seriously interfere with the general course of digestion, especially if as urged above the several digestive processes are more or less dependent on each other, it must be remembered that the sugar into which starch is changed by digestion is maltose, while cane sugar appears to be either absorbed as cane sugar or at most only inverted. Moreover if our laboratory experiments truly represent the digestion taking place in the living body, only part of the starch, § 198, is changed into maltose, while part becomes some variety of dextrine or of starch. Our knowledge of sugars and of their fate in the economy is too imperfect for us to be able to state the effects on the body of digested starch as compared with those of cane sugar or milk sugar; but that these are or may be different is shewn by the experience of medical practice. In many cases the total effect on the body of a diet from which cane sugar is as much as possible eliminated, though starch be allowed, is very different from that of one of which cane sugar forms an appreciable part.

Concerning cellulose, which in herbivora appears certainly to serve as a source of energy and to be a real food-stuff, our knowledge will not allow us to decide whether it has any special uses of its own, or whether the body is simply led to utilize and make the best of what is a necessary accompaniment of the starch of vegetable food.

Concerning the salts present in a diet we need only repeat what was said in § 526 that these, though affording of themselves little or no energy, are as essential a part of a diet as the energy giving food-stuffs, in as much as they in some way or other direct metabolism and the distribution of energy. And this is true not only of the inorganic salines such as chlorides and phosphates but also of the so called extractives. As we have seen, the presence of these bodies, both the simpler inorganic and the more complex organic salts, in the blood or in the extravascular juices or lymph of the tissues is essential to or directs or modifies the metabolic activity of the several tissues. The beneficial effects, as components of special diets, of such things as beef-tea and meat-extract, which consist chiefly of salts and extractives with a very small quantity of albumose or other forms of proteid, and the effects either beneficial or deterious of drugs both turn in common upon their taking a part of some kind or other in, it may be upon their interference with metabolic processes. The salts and extractives of a diet may be looked upon as necessary daily medicines, and a medicine as a more or less extraordinary variation in these elements of a diet.

Alcohol, to the use of which as a component of an ordinary diet special interest for various reasons attaches, comes in this class. For though observations shew that the greater part of a moderate dose of alcohol is oxidized within the body and so serves as a source of energy, man has recourse to alcohol not for the minute quantity of energy which is supplied by itself, but for its powerful influence on the distribution of the energy furnished by other things. That influence is a very complex one and cannot be fully discussed here. It is stated that moderate or small doses of alcohol diminish the consumption of oxygen and production of carbonic acid, that is to say diminish the total result of the metabolism of the body, while larger but still not intoxicating doses have a contrary effect and increase the total metabolism. But such a statement affords no sound basis for any conclusion as to the general physiological effect of alcohol, or as to its usefulness as part of an ordinary diet; it does not justify such a conclusion for example as that alcoholic drinks, taken in moderation, by diminishing metabolism economize the resources of the body. The prominent physiological problem of dietetics is not either to increase or diminish the metabolism of the body but to direct that metabolism into proper channels; and whether in each particular case a given dose of alcohol gives a right or a wrong turn to the physiological processes of the body, depends on the particular circumstances of the case. For the action of all these bodies of which we are now speaking, in contrast with the actions of the food-stuffs proper, is not only complex but variable; so complex and variable that simple experience is at present a more trustworthy guide than speculative physiology. We may add that the physiological action of alcoholic drinks is still further complicated by the fact that most such drinks contain besides ethylic alcohol, various other allied substances, whose action is even more potent than that of the ethylic alcohol itself, and whose presence very markedly determines the total effect of the drink. Such articles of diet as tea and coffee stand upon very much the same footing as alcohol.

The quantity of fluid which a man drinks or should drink daily, or more correctly the quantity of water which he should daily add to the dry solids of his diet, must vary widely according to circumstance. It will differ according as he is perspiring greatly or not, according to the nature of the dry solids of the diet, whether largely carbohydrate or not, and so on. A lower limit, below which excretion is impeded, and a higher limit, above which digestion and metabolism are injuriously affected, probably exist; but we have as yet no adequate data which will enable us to fix either of them.

§ **552**. In the selection of articles of food to supply the food-stuffs and other constituents of a normal diet, regard must of course be had in the first place to the amount of potential energy present in the material. The articles chosen for the daily fare must contain between them so much proteid, fat, and carbohydrate representing so much available energy. But it is no less important to secure that the energy potential in the material should be really available for the economy. The material must have such qualities that it is digested within the alimentary canal, and further that its digestion and absorption do not give rise to trouble either in the alimentary canal or in that secondary digestion carried on by means of the various metabolic events which we have discussed in preceding sections. A really nutritious substance is one which not only contains in itself an adequate supply of energy, but is of such a nature that its energy can be appropriated by the economy with ease or at least with as little trouble as possible. We have approximate data for determining how far an estimate of the relative usefulness of various articles of food must be corrected by allowing for the proportion of each which after an ordinary meal merely passes through the alimentary canal and the energy of which is not in any way available for the body's use. Thus a number of observations carried out on healthy individuals gave in the case of the following articles of food, the following figures as the percentage, reckoned in each case on dry material, which could be recovered from the fæces, and was therefore not digested and not used by the body:—Meat 5 p.c., Eggs 5 p.c., Milk 9 p.c., Bread (white) 4 p.c., Black Bread 15 p.c., Rice 4 p.c., Maccaroni 4 p.c., Maize 7 p.c., Peas 9 p.c., Potatoes 11 p.c. It must however be remembered that the actual correction to be made in any case will depend on the mode of cooking of the material, on the character of the meal of which it forms part and on the individual capabilities of the consumer, the latter too varying under different circumstances.

The above refers to what may be called rough digestibility, but besides this there are other circumstances to be considered. The same food-stuff in two articles of food, though actually digested, that is to say taken up by the alimentary canal, may, even while still within the alimentary canal, undergo changes in the one case differing from those in the other. A proteid may for instance in one case tend to be entirely converted into peptone, or to break up into leucin &c., or in other cases to undergo other changes; and a carbohydrate may in one case be absorbed as maltose, and in another give rise to lactic acid. Indeed, when we speak of the digestibility or the indigestibility of this or that article of food, we do not in many cases so much mean the relative amount of the substance taken up in some way or other by the alimentary canal, as the characters advantageous or otherwise of the changes which it undergoes in being so taken up.

Hence the purely chemical statement of the amount of potential energy present in an article of food is no safe guide of the physiological value of the substance. A chunk of cheese stands very high on, generally at the top of, a table of the nutritive value of articles of food drawn up on exclusively chemical principles, according to the units of energy present in a unit of the material; but it is very low down in a corresponding physiological table. And similarly a dish of old peas has a very different physiological function from a plate of fresh meat even when both contain the same amount of nitrogen.

In thus correcting for digestion the nutritive value of a diet it must also be borne in mind that the alimentary canal, while chiefly a receptive organ, is also to some extent, § 284, an excretory organ: a free passage through the canal is needed not only for carrying off undigested matter but also for getting rid of excreted matter; and the presence of the former, up to certain limits, assists the discharge of the latter. Were it possible to prepare a diet every jot and tittle of which could be digested and absorbed, the use of such a diet would probably bring about disorder in the economy, through the absence of a sufficiently rapid discharge of the matters excreted into the alimentary canal. Hence cellulose and like substances even when unutilized through absorption, are not without their use, and experience shews that digestion may be promoted by eating undigestible things.

§ **553.** The several food-stuffs of a diet may be drawn from the animal or from the vegetable kingdom. Vegetable proteids appear to undergo the same changes in the alimentary canal as do animal proteids, and the main effects on the body of proteids from the two sources seem to be the same. Our knowledge at present however is too imperfect to enable us to decide whether the functions of the two are exactly the same, whether the body behaves exactly the same upon a diet in which the proteids are exclusively of vegetable origin, as upon a diet in which, otherwise the same, the proteids are partly of animal origin also. Nor have we much better knowledge of the relative nutritive value of vegetable and animal fats. And as we have already said, we possess little or no exact knowledge as to the part played by those extractives in respect to the amount and nature of which animal food strikingly differs from vegetable food. In attempting therefore a judgment from a purely physiological point of view as to the value of an exclusively vegetarian diet compared with a diet of both animal and vegetable origin, we can do little more at present than inquire whether the former supplies the several food-stuffs in adequate quantity, in proper proportion, and in such a form as to be economically utilized by the body.

The careful examination during three separate periods of several days each of the ingesta and egesta of a man, 28 years old, weighing 57 kilos, who had for three years lived on an exclusively vegetable diet, viz. bread, fruit and oil, gave the following results.

The daily diet consisted on the average of 719 grm. solid matter and 1084 grm. water. It contained

Proteids	54 grm.	containing 8·4 N.
Fats	22 „	
Carbohydrates	557 „	(about ½ sugar and ½ starch)
(Cellulose)	16 „	

The daily fæces weighed, when fresh, 333 grm. containing 75 grm. solid matter, and were therefore both bulky and watery. There were present in the fæces fat 7 grm., starch 17 grm. and cellulose 9 grm. shewing that 30 p.c. of the fat, 6 p.c. of the starch and 56 p.c. of the cellulose had not been utilized by the body. The subject had really lived on fat 15 grm., carbohydrates 540 grm. (and cellulose 7 grm.). The fæces contained no less than 3·46 nitrogen. If we reckon the whole of this as proteid, this would give 22 grm. of undigested proteid, so that there had been a waste of 41 p.c. of the proteids, leaving only 32 grm. available for real use in the body; and indeed a very small portion only of this nitrogen can be regarded as really discharged from the body itself. The total solids of the fæces must be reckoned as partly excreta but chiefly undigested food. If we regard the 75 grm. of solid fæces as entirely undigested food, the whole solid food available for the body must be reduced from 719 grm. to 644 grm.

The urine of the day contained 5·33 grm. nitrogen; this added to the 3·46 grm. nitrogen in the fæces gives 8·79 grm. nitrogen in the total egesta as compared with the 8·4 grm. nitrogen of the food, indicating a slight loss of nitrogenous material from the body; but if we suppose that all the nitrogen in the fæces was not in the form of undigested food we may neglect this; and indeed the subject of the observation was in apparently good health and stationary weight.

Compared with either of the normal diets given in § 550 the above diet is striking for the low amount of proteids and of fats and the relative excess of carbohydrates. But though such a diet may be taken as perhaps fairly typical of the daily food of a rigid vegetarian, a much more richly proteid diet may be obtained from sources still strictly vegetable. Thus the diet, entirely vegetable in nature, of an average Japanese labourer of about the same weight as the individual whose data we have just given has been estimated to consist of Proteids 102 grm., Fat 17 grm., Carbohydrates 578 grm. And the diet of a Roumanian peasant, living chiefly on beans and maize with the addition of fat of some kind, has been calculated to furnish no less than Proteids 182 grm., Fat 93 grm., Carbohydrates 968 grm.; but the real nutritive value of such a diet must need very large correction indeed. Cf. § 552.

The examination of the diet of an individual living with a fair nitrogenous equilibrium and apparently good health on a modified vegetable diet, that is to say one which included milk and eggs, gave the following: Proteids 74 grm., Fat 58 grm., Carbohydrates 490 grm., a diet which differs from the normal diet almost solely in the lesser amount of proteids, one third of which by the bye was supplied by the animal material, eggs and milk. In another instance, nitrogenous equilibrium and fairly good health were secured, for some weeks at all events, on a vegetable diet yielding Proteids about 100 grm., Fats 70 grm., Carbohydrates 400 grm.; but in this nearly the whole of the fat was furnished by the animal product butter, and Liebig's extract was freely used.

Confining ourselves however to the more strictly vegetarian diet, we may conclude in the first place that, unless the daily food be very large in amount, the proteid element of such a diet falls considerably below the 100 or more grm. given in the normal diet. But we cannot authoritatively say that such a reduction is necessarily an evil; for as we stated above, § 550, our knowledge will not at present permit us to make an authoritative exact statement as to the extent to which the proteid may be reduced without disadvantage to the body when accompanied by adequate provision of the other elements of food; and this statement holds good whether the body be undertaking a small or large amount of labour. A second feature of such a diet is the marked reduction of the fat and its replacement by carbohydrates. Although here again we cannot make a distinctly authoritative statement, the evidence which we possess bears clearly in the direction that such a reduction is a marked disadvantage. A third and very characteristic feature of the strictly vegetarian diet is the relatively large amount of undigested food lost to the body and discharged as fæces. Even when the diet is scanty, so that the proteid element is low, the amount of fæces relatively to the total food is high; and when a more normal proteid contribution is secured by ample meals the fæces become exceedingly voluminous. Indeed when, leaving man, we compare the herbivorous with the carnivorous mammal, we find that the former is almost as clearly distinguished from the latter by its frequent and abundant fæces as by the anatomical features of its organization. We have already urged that, since the fæces serve as a means of excretion of the real waste products of metabolism, a certain amount of vehicle to carry these away is of advantage or even necessary; but there are no facts at present known to us, which shew that the larger intestinal current of the purely vegetable diet effects any such good as can compensate for the obvious waste of labour incurred in its transport and management, to say nothing of the opportunities of mischief offered by a mass of material more subject to the dominion of foreign organisms than even to that of the body itself, though these opportunities are less than with a corresponding mass of animal origin. With respect to these three features then, the strictly vegetarian diet seems, on physiological grounds inferior to one of a mixed nature. There are as we said other aspects, still of a strictly physiological kind, to be considered, such as the relative digestibility of vegetable articles of food, the relative metabolic value of the food-stuffs of vegetable origin, and the influence of animal extractives; but any fuller discussion of these points would be out of place here.

§ **554**. We have treated the diet discussed above as a normal diet, suitable for man under ordinary or general circumstances. Ought such a diet to be modified for the various exigences of life such as labour, age, climate, and the like?

We shall discuss the influence of age in the concluding portions of this work.

We may be inclined at first sight to assume that the total amount of the diet should vary with the weight, that is the size of the individual; and indeed in discussions on nutrition, statements concerning metabolism and amount of food are often given in terms of per kilo of body weight. In a broad sense it may be true that a small man needs less food than a large one; but it must be remembered that, as we saw in speaking of animal heat, the smaller organism, having the relatively larger surface, carries on a more rapid metabolism per unit of body weight, and so needs relatively more food. And moreover the influence of size is probably far less than the influence exerted by the inborn individual characters of the organism, giving rise to what we may call the personal equation of metabolism. The smaller metabolism of woman, leading to the use of a scantier diet, as compared with that of man, is to be regarded in this light rather than with reference to the average lesser weight of woman. The relative metabolism of the two sexes may be illustrated by the case of an active man and his wife, both of about the same age and weight, the man being rather the heavier and the woman rather the older, who, in carrying out together an experiment on the relative values of vegetable and animal food, both lived for some time on the same kind of diet, and found that nutritive equilibrium was, in the one case and in the other, maintained when

	Proteids.	Fats.	Carbohydrates.
The man consumed daily about	100	70	400
The wife „ „ „	60	67	340

The most striking difference is in the proteids.

§ **555**. With regard to climate the chief considerations attach to temperature. When the body is exposed to a low temperature the general metabolism of the body is increased owing to a regulative action of the nervous system, § 534. We might infer from this that more food is necessary in cold climates; and, since the increase in the metabolism appears to manifest itself chiefly in a greater discharge of carbonic acid and therefore to be especially a carbon metabolism, we might infer that the carbon elements of food should be especially increased. When the body is exposed to high temperatures the same reflex mechanism tends to lower the metabolism; but the effects in this direction are much less clear than those of cold, and soon reach their limits; the bodily temperature is maintained constant under the influence of surrounding warmth not so much by diminished production as by increased loss. We may infer from this that in warm climates not less but if anything rather more food than in temperate climates is necessary in order to supply the perspiration needed for the greater evaporation and discharge of heat by the skin.

In both cold and warm climates however man trusts much more to variations in his clothings and immediate surroundings to protect him against cold or to guard him from heat than to any marked variations in his normal diet. In the former he may perhaps be expected to eat somewhat more, since, in spite of wrappings, his skin still feels in part the cold, and thus the nervous mechanism for the increase of metabolism is to a certain extent set to work. And since the metabolism thus increased appears to affect especially the carbon of the body, he may further be expected to increase the fats rather than the carbohydrates of his food seeing that the former supply him with the most energy for their weight. But it is very doubtful whether what he might thus be expected to gain over a corresponding increase in carbohydrates is not more than counterbalanced by the increased labour of digestion; and the habits of the dwellers in arctic climates cannot safely be taken as guides in this matter, for their reputed love of fat is probably the result of that being their most available form of carbon. Indeed the evidence that the increase of metabolism provoked by cold bears exclusively on carbon constituents is so uncertain that it may be doubted whether any change in the normal diet, beyond some increase in the whole, should be made to meet a cold climate. Similar reasons would lead one to infer that man in the warmer climate would maintain on the whole the same normal diet, the only change perhaps being to increase it slightly, possibly throwing the increase chiefly on the carbohydrates with the special view of furthering perspiration.

§ **556**. A special diet for the purpose of fattening, that is to say for the accumulation of adipose tissue out of proportion to the rest of the body, is not needed in the case of man. The power to store up fat in adipose tissue is much more dependent on certain inborn qualities of the organism which we cannot at present define than on the kind of food; of two bodies living on the same diet, and under the same circumstances, one will become fat while the other will remain lean; and it is an object of the agriculturist to develope by breeding and selection a "constitution" which will store up the most fat on the cheapest diet. In fattening animals, the chief care, when the selection of the kind of animal has been made, is to provide adequate carbohydrate food, which as we have seen is the chief fattener; and the object of the farmer in rearing stock for the butcher is mainly to convert cheap vegetable carbohydrate into dear animal fat. Further aids in fattening may be found in providing repose for the body of such a kind that, while sufficient energy is expended to secure adequate digestion and absorption of food, all causes leading to an increase of metabolism, by which energy is set free and leaves the body, are avoided as much as possible.

To avoid fat rather than to increase it is often an object of human care. This may be effected by diminishing fats and carbohydrates, but also, in a very marked manner, by relatively increasing the proteids. Proteid food as we have seen augments the whole metabolism of the body, hurrying on the destruction not only of proteid but of carbon food; and a tendency to corpulency may be counteracted by a diet in which fats and carbohydrates are much restricted, and proteids are largely increased. When, as in what is known as the Banting method, the diet is almost exclusively proteid, the nitrogenous overwork entails dangers on organisms which do not possess the power of ridding themselves freely of the large amount of nitrogenous waste which such a diet produces. A less severe method in which the fats and carbohydrates are diminished only, not entirely done away with, and the proteids only moderately increased, is less open to objection; and such a diet, assisted by other hygienic conditions, has proved successful.

An increase of daily food, largely proteid in nature, given under circumstances, such as a large amount of passive exercise and skin stimulation, known as 'massage', which will not only favour digestion but also promote metabolism in general, may be given, with favourable results. In this way, an enormous metabolism may be excited, and yet so carried on that the body gains both in flesh and in fat. Thus, in one case, the patient with an initial weight of 45 kilos, and a daily nitrogenous metabolism, calculated as 28 grm. proteid, reached in the course of about 50 days a weight of 60 kilos, the daily nitrogenous metabolism being raised on one occasion to 182 grm. proteid, with an average on the whole period of 150 grm. During the treatment no less than 8420 grm. of proteid were taken as food.

§ **557**. With regard to labour, since as we have seen the energy expended as work done is not taken out of and away from the amount set free as heat, the two forms of energy being so related that an increase of work done is accompanied by a greater or less increase of heat set free, it is obvious that a man who is doing a hard day's muscular work needs a larger income of energy for the day than does an idle man. What we have learnt concerning muscular metabolism further shews us that the additional energy needed is not necessarily to be supplied by an increase in the proteid components of the diet; the energy of muscular contraction does not come as was once thought from proteid metabolism (§ 529). The fact that it is the carbon metabolism which is augmented in muscular work may suggest that the extra food for extra work should be exclusively carbon compounds; and if, as seems probable, the carbohydrates are more readily and directly available for the functional metabolism of muscle than are the fats, we might be further led to recommend an increase in carbohydrates to form a diet especially suited for labour. But several considerations should make us hesitate before we come to such a conclusion. A muscle is not a machine within the body which can be loaded and fired off irrespective of the rest of the body. In the performance of muscular labour, the condition of the muscle, the amount of energy available in the muscle itself, is of course of prime importance; but, and this perhaps especially holds good in severe labour, of great importance also, we might almost say of no less importance, is as we have urged (§ 390) the power of the body as a whole to avail itself of the energy latent in the muscle. The power of doing work hangs not on the muscle alone, but on the heart, the lungs, the nervous system and indeed on the whole body. It is very doubtful whether we ever, even in supreme efforts, draw upon more than a portion of the capital of energy lodged in the muscle itself; fatigue is far more a nervous than a muscular condition, and even the distinctly muscular fatigue is as we have seen (§ 86) partly at least the result of the accumulation of products and not alone the using up of available energy. In choosing a diet for muscular labour we must have in view not the muscle itself but the whole organism. And though it is possible that future research may suggest minor changes in the various components of a normal diet such as would lessen the strain during labour on this or that part of the body, on the muscles as well as on other organs, our present knowledge would rather lead us to conclude that what is good for the organism in comparative rest is good also for the organism in arduous work, that the diet, normal for the former condition, would need for the latter a limited total increase but no striking change in its composition. In preparing the body for some coming arduous labour in "training" as it is called, an increase of proteid food, for the purpose of hurrying on the general metabolism of the body, and thus of making 'new flesh' and renovating the body, so to speak, in view of the strain to be put upon, may perhaps suggest itself; but even this is doubtful.

The principles of such a conclusion with regard to muscular work may be applied with still greater confidence to nervous or mental work. The actual expenditure of energy in nervous work is relatively small, but the indirect influence on the economy is very great. The closeness and intricacies of the ties which bind all parts of the body together is very clearly shewn by the well known tendency of so called brain work to derange the digestive and metabolic activities of the body; and if there be any diet especially suited for intellectual labour it is one directed not in any way towards the brain, but entirely towards lightening the labours of and smoothing the way for such parts of the body as the stomach and the liver.

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